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DISTANT NEUROANATOMIC COMPLICATIONS OF SPINA BIFIDA (SPINAL DYSRAPHISM)

HYDROCEPHALUS, ARNOLD-CHIARI DEFORMITY, STENOSIS OF THE AQUEDUCT OF SYLVIUS, ETC.; PATHOGENESIS AND PATHOLOGY

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In a previous article [1] I emphasized that spina bifida is primarily an expression of inadequate or improper fusion of the embryonal tissues in the dorsal median region of the developing embryo and the resultant pathologic states are manifested, therefore, in the cutaneous, mesodermal and/or neural derivatives of these tissues. Since to many the term spina bifida indicates a vertebral defect (posteriorly through the arch or anteriorly through the bodies of the vertebrae or through the sacrum), and since in many instances anomalies, particularly neural in nature, belonging to the spina bifida group of disorders occur unassociated with evidences of a bony defect, the generic term "spinal dysraphism" was used to identify these conditions resulting from defective raphe formation. In that study the cutaneous, vertebral, meningeal and neural manifestations of the dysraphic state were described. Just as important, however, are the pleomorphic neuroanatomic changes in distant parts of the nervous system resulting from this spinal anomaly.

In the early stages of human fetal development the spinal cord extends to the lowermost portion of the sacrum and the spinal nerve roots pass horizontally, escaping through their respective intervertebral foramens (fig. 1). Since the growth of the spinal column is of greater magnitude than that of the spinal cord, changes in the topographic relation between these two structures soon occur. As the brain is more

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1. Lichtenstein, B. W.: "Spinal Dysraphism," Spina Bifida and Myelodysplasia, Arch. Neurol. & Psychiat. **44**:792 (Oct.) 1940.

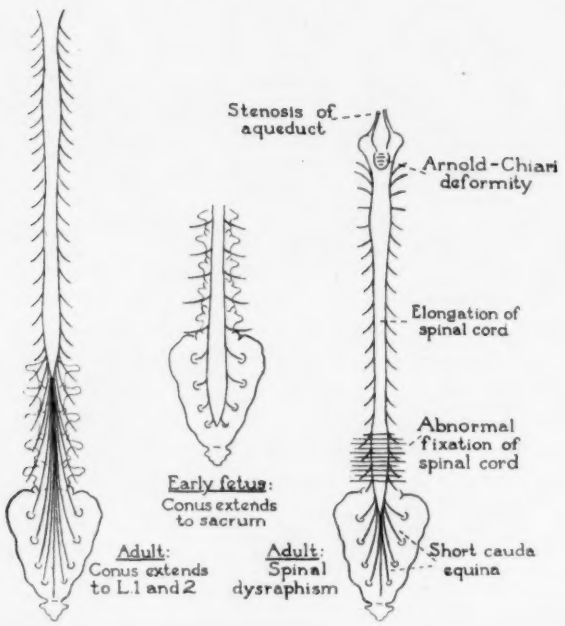
Stenosis of aqueduct
Arnold-Chiari deformity
Elongation of spinal cord
Abnormal fixation of spinal cord
Short cauda equina
Early fetus: Conus extends to sacrum
Adult: Conus extends to L.1 and 2
Adult: Spinal dysraphism

Fig. 1.—Schematic drawing illustrating the relation of the spinal cord and its roots to the vertebral column in an early stage of fetal development, in an adult and in a theoretic case of spina bifida with fixation of the spinal cord (see text).

Fig. 2.—Low power photomicrograph through the cutis and the spinal cord at the site of a vertebral and dural defect. The spinal cord at this level reveals the diastematomyelic type of duplication (see text). One of the cords is fixed to the subcutis, while the pia mater of the other is fused with the subcutaneous tissues. Weil myelin sheath stain, counterstained by the Van Gieson method.

securely fixed to its surrounding structures than the spinal cord, a relative rostral migration of the latter occurs. This results in the final localization of the conus medullaris in the vicinity of the first or second lumbar vertebra, the caudal deviation of the spinal nerve roots becoming more marked as the lumbosacral portion of the spinal cord is reached, and the development of the cauda equina.

In some cases of spinal dysraphism the normal relation of the spinal cord, its meninges and nerve roots to the surrounding tissues is disturbed. In some instances there is actual fixation of the spinal cord to the cutis (fig. 2), and this precludes its adequate rostral migration. In other instances the fixation is not so exquisite; only the meninges or the spinal nerve roots are anchored to the surrounding tissues. The distant neuroanatomic complications are dependent on the degree and extent of the fixation, as well as on the readjustment of the neural structures to an altered environment. The neuroanatomic alterations resulting from this abnormal fixation of the spinal cord are schematically represented in figure 1.

NEUROANATOMIC CHANGES

Cauda Equina.—Since the cauda equina develops as the result of the ascent of the conus medullaris to the level of the first or second lumbar vertebra, an arrest in this ascent will result in its being abnormally short. This was early recognized by Ranke [2] and by von Recklinghausen,[3] who noted that in some instances of spina bifida the spinal cord extended to the sacrum. This observation is of clinical significance, for spinal puncture performed at the usual site may result in injury to the spinal cord. Beck [4] advised caution in making spinal punctures in cases in which spina bifida occulta is suspected.

Spinal Cord.—If the fixation of the spinal cord is such as to preclude any change in its topographic relation to its neighboring vertebrae, that portion above the site of fixation must necessarily become elongated and/or migrate caudally. Of these two processes, the latter is most in evidence, for in many instances the first cervical spinal segment may be displaced as low as the fourth or fifth cervical vertebra and the emerging cervical spinal nerve roots pass diagonally upward and lateralward, like those of the spinal accessory nerve, to escape through their respective intervertebral foramens. That the spinal cord is elongated or stretched is evident by its sudden ascent when the fixation is relieved

2. Ranke, H.: Zur Aetiologie der Spina bifida lumbalis und lumbosacralis, Jahrb. f. Kinderh. **12**:116, 1878.

3. von Recklinghausen, F.: Untersuchungen über die Spina bifida, Virchows Arch. f. path. Anat. **105**:243, 1886.

4. Beck, O.: Spina bifida occulta und ihre ätiologische Beziehung zu Deformitäten der unteren Extremität, Ergebn. d. Chir. u. Orthop. **15**:493, 1922.

either surgically or at necropsy. Katzenstein's [5] theory that the stretching of the spinal tissue may result in degeneration may be applicable in some of these cases in which symptoms of involvement of the spinal cord develop later in life.

Hindbrain.—In 1894 Arnold [6] described a curious malformation of the hindbrain occurring in a case of spina bifida, and in the following year Chiari [7] more fully described the malformation in a series of 7 cases of spina bifida. Prior to this Chiari,[8] in 1891, had noted an isolated instance in which the fourth ventricle extended downward to the fifth cervical vertebral segment. In 1907 Schwalbe and Gredig [9] gave a detailed description of this deformity and called it the Arnold-Chiari malformation, under which term it has continued to be designated in the literature. This deformity has been described as a downward migration of the hindbrain with protrusion of the lowermost portion of the cerebellum and medulla oblongata through the foramen occipitale magnum into the vertebral canal. The upper cervical portion of the spinal cord is also dislocated downward, as aforementioned.

(*a*) Cerebellum: The changes in the cerebellum (the Arnold malformation) are pleomorphic. They may vary from hypoplasia of the hemispheres to dysplasia of the folia or may include both. In Jacob's [10] case the infant at birth had hydrocephalus, spina bifida, meningocele and bilateral clubfoot. Necropsy revealed the cerebellum to be abnormally small and to be located abnormally deep in the vertebral canal, and microscopic studies showed marked malformation of some of its folia. In Bruns's [11] case 6, that of a 2 month old child with lumbosacral spina bifida and hydrocephalus, there were partial symmetric dysgenesis of the ventrocaudal portions of the cerebellar hemispheres and milder dysgenesis of the lower part of the vermis. In his case 7,

5. Katzenstein, M.: Beitrag zur Pathologie und Therapie der Spina bifida occulta, Arch. f. klin. Chir. **64**:607, 1901.

6. Arnold, J.: Myelocyste, Transposition von Gewebskeimen und Sympodie, Beitr. z. path. Anat. u. z. allg. Path. **16**:1, 1894.

7. Chiari, H.: Ueber Veränderungen des Kleinhirns, des Pons und der Medulla oblongata infolge von kongenitaler Hydrocephalie des Grosshirns, Denkschr. d. Akad. d. Wissensch. Math.-Naturw. Cl. **63**:71, 1895.

8. Chiari, H.: Ueber Veränderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns, Deutsche med. Wchnschr. **17**:1172, 1891.

9. Schwalbe, E., and Gredig, M.: Ueber Entwicklungsstörungen des Kleinhirns, Hirnstamms und Halsmarks bei Spina bifida, Beitr. z. path. Anat. u. z. allg. Path. **40**:132, 1907.

10. Jacob, H.: Ueber die Fehlentwicklungen des Kleinhirns, der Brücke, und des verlängerten Marks (Arnold-Chiarische Entwicklungsstörung) bei kongenitaler Hydrocephalie und Spaltbildung des Rückenmarks, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:229, 1939.

11. Bruns, R.: Zur Kenntnis der Bildungsfehlen des Kleinhirns, Schweiz. Arch. f. Neurol. u. Psychiat. **3**:13, 1918.

that of a 3 month old infant with lumbosacral spina bifida and internal hydrocephalus, the cerebellum was generally hypoplastic, the left lobe was smaller than the right and the whole organ seemed to have been pulled in a frontocaudal direction.

(*b*) Medulla Oblongata and Pons: Frequently the cerebellum shows minimal changes, but the medulla oblongata and pons are displaced caudally (the Chiari malformation). Because the dorsal part of the spinal cord is the portion usually fixed to the surrounding structures (fig. 2), the ascent of the spinal cord may not occur on a uniform plane. The ventral, unfixed portion, ascending to a greater degree than its dorsal portion, results in an unequal descent of the hindbrain and the cervical portion of the spinal cord. To compensate for the unequal ascent the dorsal portion of the medulla migrates downward to a greater degree than its ventral portion. This results in distortion of the hind end of the fourth ventricle and in the development of a protrusion on the dorsum of the medulla, which may resemble a tumor but which is really a manifestation of its internal derangement.

In addition to alterations in the cerebellum, pons and medulla oblongata, significant changes occur in the choroid plexus of the fourth ventricle, the aqueduct of Sylvius and the lowermost cranial nerves in some cases.

REPORT OF CASES

From a large source of material I have selected several cases illustrating the important neuroanatomic complications of the spinal dysraphic state. Since the development of hydrocephalus is probably the most important complication of spinal dysraphism, I shall emphasize the changes in the brain rather than the abnormalities in the spinal cord or the cauda equina.

In an effort to simplify a complicated subject the changes in and about the spina bifida defect will be classified as the primary pathology, the neuroanatomic complications as the secondary pathology and the accidenal inflammatory changes, when present, as the complicating pathology. As in my first article on spina bifida,[1] the primary pathology will be described in terms of the cutaneous, mesodermal (vertebral and dural) and neural forms of spinal dysraphism.

CASE 1.—*History.*—A white female infant was born with lumbosacral spina bifida. Later slowly progressive internal hydrocephalus developed, and the meningocele sac became infected. Death resulted from suppurative meningitis at 3 months of age.

Primary Pathology.—Summary: Spina bifida cystica lumbosacralis was present. No evidence of primary cutaneous dysraphia was noted. Mesodermal dysraphia was present in the form of vertebral dysplasia, with defect in the arches of the lowermost thoracic and all the lumbosacral vertebrae, and dural dysplasia,

consisting of nonclosure of the dura mater dorsal to the cord in the region of the bony defect. The neural dysraphia was obscured by complicating pathologic changes.

Gross Examination: Over the lowermost thoracic and all of the lumbar vertebrae, in the midline of the back, was a spherical cystic mass, measuring 5 by 4 by 2 cm. The skin over the central portion was a deep purple-red and was covered with a purulent exudate. Pressure on the mass resulted in the escape of purulent cerebrospinal fluid through minute defects in the area of hemorrhage. On cutting through the meningocele the lumbosacral portion of the spinal cord was seen to be firmly adherent to the subcutis. In places the spinal cord was atrophic as a result of the pressure within the meningomyelocele sac.

Secondary Pathology.—Summary: The Chiari deformity, stenosis of the aqueduct of Sylvius and hydrocephalus of the lateral and third ventricles were present.

Gross Examination: Important changes were seen during the performance of the necropsy. After removal of the spines and arches of all the vertebrae but

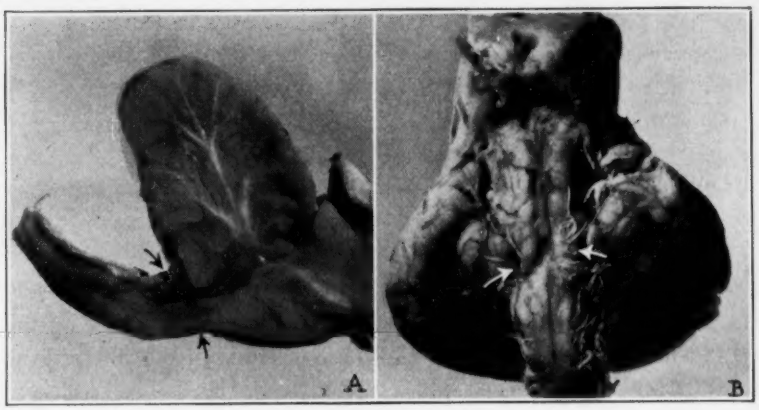

Fig. 3.—*A*, midsagittal section through the hindbrain in case 1. *B*, ventral aspect of the hindbrain in case 1. The site of the arch of the atlas is indicated by arrows. Note the elongation of the pons and the localization of the medulla oblongata below the foramen magnum.

the first cervical and the squamous portions of both occipital bones, the arch of the atlas was seen to constrict sharply the dural sac. Immediately the arch of the atlas was cut the dural sac bulged outward. The dura mater was then incised. The brain stem almost completely filled the vertebral canal in the region of the atlas and the axis, and a constriction ring was clearly seen at this point. When the spinal cord was severed through the midcervical region, the entire brain stem suddenly moved upward, as though it had previously been tied down. The uppermost cervical spinal nerve roots ran upward to escape through their respective intervertebral foramens. The brain and spinal cord were then removed and fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. After fixation the hindbrain and the upper cervical portion of the spinal cord were cut in a midsagittal plane (fig. 3). The fourth ventricle was elongated downward, was very narrow and extended deep into the vertebral canal. The

lower portion of the vermis cerebelli, the choroid plexus of the fourth ventricle and the medulla oblongata were all compressed at the site of the arch of the atlas. The constriction ring on the brain stem is indicated by arrows in figure 3. The pons did not have its normally round contour but was narrow and elongated, extending downward to the level of constriction. The medulla oblongata was entirely below the level of the foramen magnum. These changes are well seen in a low power photomicrograph through this area (fig. 4). The constriction of the brain stem at the pontomedullary junction is indicated by arrows. In this plane the olivary bodies below the constriction are barely seen. The fourth ventricle is narrow, and parts of the inferior portion of the vermis and tufts of choroid plexus of the fourth ventricle are all crowded together. The midbrain,

Fig. 4.—Low power photomicrograph in a parasagittal plane through the hindbrain. The site of the arch of the atlas is indicated by arrows. The pontomedullary junction is compressed, and the medulla oblongata is located below the foramen magnum. *C.P.* indicates the choroid plexus of the fourth ventricle, and *Oliv* the olivary body. Stain same as that in figure 2.

like the hindbrain, is greatly elongated, and the aqueduct of Sylvius, elongated in an anteroposterior direction, is narrow. In figure 5 the aqueduct in this case may be compared with the iter in the brain of a normal infant. The stenosis of the aqueduct resulted in hydrocephalus of the lateral and third ventricles. Figure 6*B* is a low power photomicrograph showing the atrophy of the cerebral cortex resulting from hydrocephalus.

Complicating Pathology.—The spinal cord, attached to the subcutis, revealed pressure atrophy and inflammatory changes. There was marked suppurative leptomeningitis throughout the length of the spinal cord and the medulla oblon-

gata up to the constriction at the foramen magnum and less intense inflammation over the other portions of the brain. The lower thoracic levels of the spinal cord, like the lumbar portion, were the site of suppurative myelitis (fig. 6*A*). The lateral, third and fourth ventricles were filled with pus (pyocephalus), and the ependymal lining was everywhere hemorrhagic and ulcerated (fig. 6*B*).

Fig. 5.—Compare the aqueduct of Sylvius of the infant in case 1 (*A*) with the aqueduct of a normal infant of the same age (*B*). Weil myelin sheath stain.

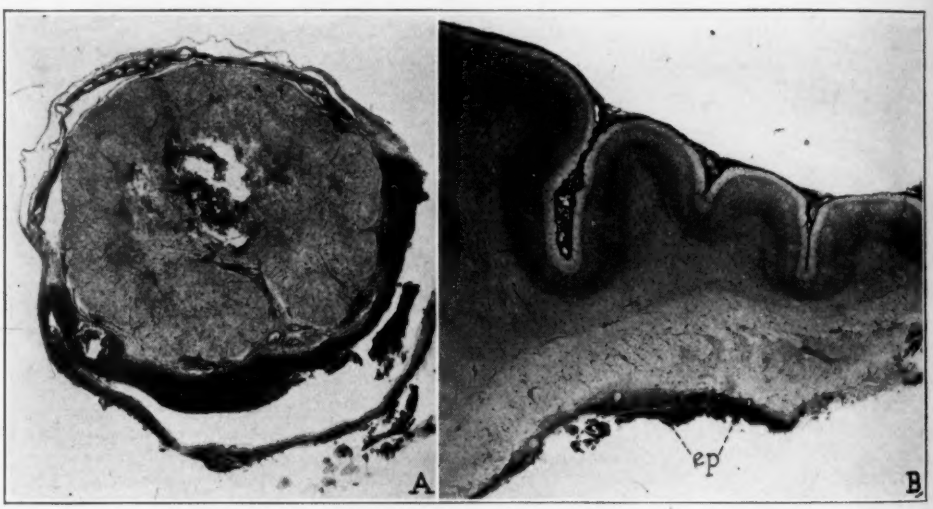

Fig. 6.—Low power photomicrographs showing (*A*) the suppurative spinal leptomeningitis and the intramedullary suppuration near the site of the vertebral and meningeal defect and (*B*) the suppurative ependymitis in the lateral ventricles; *ep* indicates area of ependymitis. Toluidine blue stain.

The primary pathology in this case was the spinal dysraphic state in the lowermost thoracic and the lumbosacral region. This was characterized by a marked posterior vertebral defect (spina bifida) and a

dural defect (dural araphia), and as a result the spinal cord was adherent to the overlying skin. This fixation of the spinal cord precluded its adequate ascent, resulting in a downward migration of the midbrain, the pons, the medulla oblongata and the upper cervical segments of the spinal cord. The medulla oblongata and the foramens of Luschka became localized below the level of the foramen magnum. As the tentorium cerebelli precluded downward migration of the forebrain, the midbrain was stretched by the traction from below, producing stenosis of the aqueduct of Sylvius. The relative stenosis of the latter resulted in the hydrocephalus of the third and the lateral ventricles. The meningocele sac then became infected from an infection in the overlying ulcerated epidermis. This produced local suppurative myelitis at the site of the spina bifida and diffuse suppurative spinal leptomeningitis. The infection, extending up to the level of the constriction, entered the fourth ventricle through the foramens of Luschka and spread through the ventricular system, producing suppurative ependymitis and pyocephalus. The ependymal inflammation was much more marked than the cerebral leptomeningeal inflammatory changes.

Case 2 (which I have permission from Drs. H. Josephy and R. P. Mackay to report).—*History.*—In a white female infant lumbosacral spina bifida and hydrocephalus were noted at birth. The lumbosacral mass was cystic and measured 8 cm. in length and 4 cm. in greatest width. The child fed poorly; the head became progressively larger; she became lethargic and died at the age of 7 months.

Primary Pathology.—Summary: Spina bifida cystica lumbosacralis and cutaneous dysplasia in the nature of hypoplasia of the skin and hypertrichosis were present. Mesodermal dysplasia existed in the nature of posterior vertebral dysplasia (spina bifida) and dural araphia. Neural dysplasia in the nature of pseudoduplication of the spinal cord, or so-called diastematomyelia (fig. 2), was noted.

Gross Examination: The back over the lower part of the spine was the site of a defect in the form of spina bifida cystica. The mass measured 8 by 4 cm., and the skin over it was ulcerated in places. The skin about the sac was the site of increased growth of hair. The neural arches from the eleventh thoracic vertebra downward to the tip of the sacrum were open. The spinal cord and its nerve roots in this region were firmly adherent to the walls of the sac.

Microscopic Observations: At the site of the dysraphic defect the spinal cord presented a type of pseudoduplication commonly known as diastematomyelia (fig. 2). The pia mater of one of the spinal cords was attached to the cutis by a band of connective tissue, whereas the medullary substance of the other was directly adherent to the under surface of the skin. This exquisite fixation of the neural elements resulted in the following secondary pathology.

Secondary Pathology.—Summary: There were Arnold-Chiari deformity of the hindbrain, stenosis of the aqueduct of Sylvius and internal hydrocephalus of the lateral and third ventricles.

Gross Examination: The head was greatly enlarged; the fontanels were open, and the cerebral ventricles contained about 3,000 cc. of clear cerebrospinal fluid. The septum pellucidum was destroyed, the lateral ventricles being in free com-

munication with a widely dilated third ventricle. The aqueduct of Sylvius was narrow, elongated and collapsed from side to side. The cerebellum appeared to be of normal size. The pons was elongated, its lower border reaching the level of the foramen magnum. The entire medulla oblongata was located below the level of the atlas in the vertebral canal. The fourth ventricle was narrow and extended downward to the level of the fourth cervical vertebra.

Microscopic Observations: The brain was fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. and after fixation was cut coronally except for the hindbrain, which was cut in a midsagittal plane. Figure 7 is a low power photomicrograph of such a section of the hindbrain. The site of the atlas is indicated by an arrow. It is apparent that the entire medulla oblongata is located in the vertebral canal. The roof of the fourth ventricle is the distorted and compressed

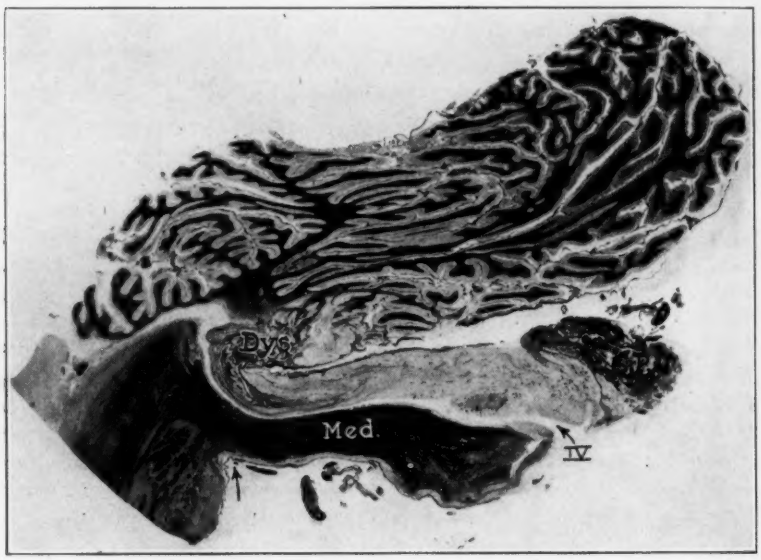

Fig. 7.—Low power photomicrograph of a midsagittal section through the hindbrain in case 2. The site of the foramen magnum is indicated by the arrow. The medulla oblongata extends far into the vertebral canal. *Dys.* indicates dysplastic cerebellar folia; *Med.*, medulla oblongata; *C.P.*, choroid plexus of the fourth ventricle, and *IV*, the fourth ventricle. Stain same as that in figure 2.

inferior portion of the vermis. The choroid plexus of the fourth ventricle is also located deep in the vertebral canal. Under high magnification the cellular disorganization in the Purkinje and Bergmann cell layers is striking. Sections through the midbrain revealed the aqueduct of Sylvius to be everywhere patent, free from inflammatory changes but narrowed laterally and greatly elongated from its origin in the widely dilated third ventricle to its exit in the elongated and compressed fourth ventricle.

As in the first case, the primary pathologic change was a marked spinal dysraphic state, characterized by the mesodermal manifestations of spinal dysraphism, namely, defects in the arches of the lumbosacral

vertebrae and dural araphia (nonclosure of the dura mater dorsal to the spinal cord). The spinal cord at the level of the bony defect showed a marked degree of neural dysraphism in the form of of pseudoduplication of the spinal cord—diastematomyelia. The fixation of the spinal cord and its leptomeninges to the cutis precluded its rostral migration, and this resulted in downward traction of the midbrain, hindbrain and cervical portion of the spinal cord. The stenosis of the aqueduct of Sylvius played a role in the development of the hydrocephalus of the lateral and third ventricles. The pons and medulla oblongata were elongated and pulled downward (the Chiari deformity), and the choroid plexus of the fourth ventricle also lay deep in the vertebral canal. Some folia of the vermis cerebelli were also pulled downward and showed

Fig. 8.—Photographs of the hindbrain in case 3, showing a portion of the vermis cerebelli in the fourth ventricle. *C* indicates the cerebellar protrusion.

marked disorganization of their architectonics (Arnold malformation). The impaction of the hindbrain in the foramen magnum also played a role in the development of the hydrocephalus, as it precluded the proper escape of the cerebrospinal fluid from the fourth ventricle and its passage over the brain stem. The fourth ventricle was not dilated.

CASE 3.—In this case the Arnold-Chiari deformity was much more complicated than the deformities in the previous 2 cases.

History.—In a white female infant born with a lumbosacral spina bifida and meningocele progressively increasing hydrocephalus developed. She died at 6 months of age. The meningocele measured 9 by 7 by 5.5 cm. in its greatest diameters.

Primary Pathology.—Summary: Spina bifida cystica lumbosacralis was present. As in the 2 previously described cases, there was a marked defect in the arches

of the lumbosacral vertebrae, and the dura mater in this region passed laterally to fuse with the connective tissue in the subcutis, as described in one of my previous papers.[1] The importance of this case lies in the secondary changes in the brain stem and the upper cervical portion of the spinal cord.

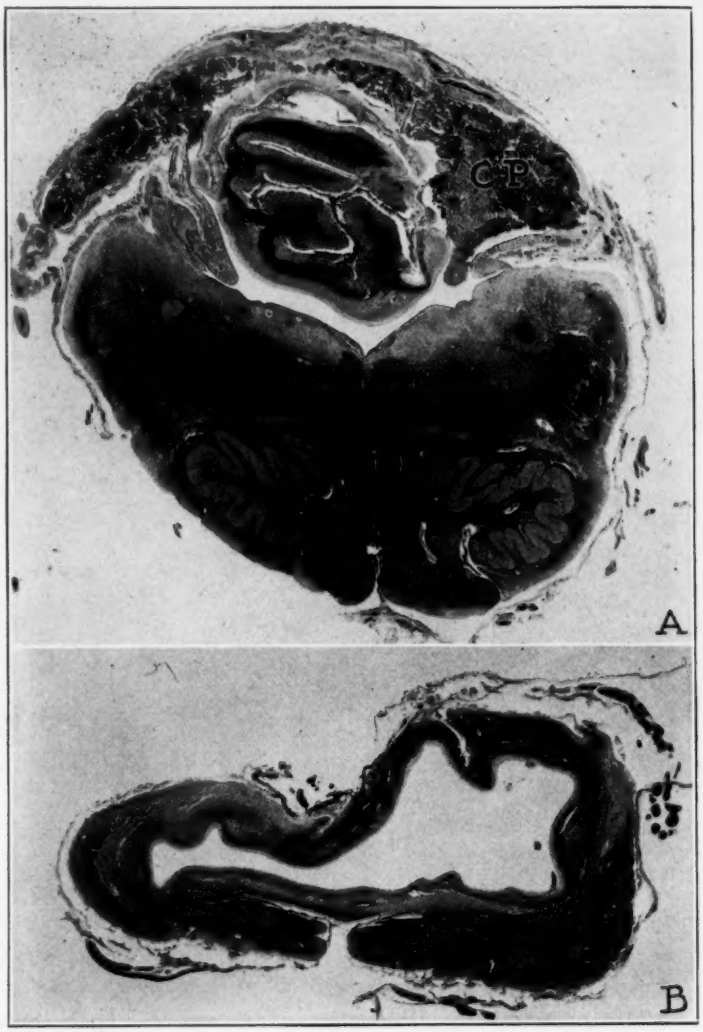

Fig. 9.—*A*, low power photomicrograph through the medulla oblongata and part of the cerebellum located in the vertebral canal. *C.P.* indicates the choroid plexus of the fourth ventricle. *B*, low power photomicrograph through the uppermost cervical level of the spinal cord, showing the pseudosyringomyelic cavity dorsal to the central canal. Stain same as that in figure 2.

Secondary Pathology.—Stenosis of the aqueduct of Sylvius, internal hydrocephalus of the lateral and third ventricles and Arnold-Chiari deformity were present.

Gross Examination: The brain was moderately enlarged, and the leptomeninges over the cerebral cortex were thin and transparent. The tips of the temporal lobes were ballooned, and the cortex in this region was thin. Coronal sections of the formaldehyde-fixed brain revealed the lateral and third ventricles to be greatly dilated. The septum pellucidum was very thin and was the site of the large

Fig. 10.—Low power photomicrograph through the hindbrain of the same magnification as that in figure 9 *A*. The medulla is elongated and narrow, and many of the cerebellar folia are dysplastic. *Dys.* indicates dysplastic cerebellar folia. Stain same as that in figure 5.

defects. The foramens of Monro were widely dilated, the enlarged lateral ventricles communicating with the dilated third ventricle. The midbrain was elongated and the aqueduct of Sylvius collapsed from side to side. The cerebellum was grossly normal. Most of the medulla oblongata was located beneath the foramen magnum in the vertebral canal. On cutting through the medullary substance at the level

of the third cervical vertebra, a lip of cerebellar substance could be seen protruding into the fourth ventricle (fig. 8). The upper cervical segments of the spinal cord were dislocated downward and on cross section were seen to contain a cavity (fig. 9 *B*). Many transverse sections were taken through the brain stem and cervical portion of the cord and were stained by appropriate methods.

Fig. 11.—Higher power photomicrograph of figure 9 *A*, showing the tufts of the choroid plexus impacted in the fourth ventricle below the level of the foramen magnum. *IV* indicates the fourth ventricle, and *C.P.*, the choroid plexus. Stain same as that in figure 5.

Microscopic Observations: A section through the hindbrain just above the foramen magnum (fig. 10) passed through the medulla oblongata above the level of the olivary bodies. The medulla at this level (fig. 10) was elongated and much smaller in transverse diameter than a lower section located in the vertebral canal

(fig. 9 *A*). The upper level shows clearly the dysplastic cerebellar folia (fig. 10). Sections through the lower portion of the medulla lying in the vertebral canal passed through the olivary bodies (fig. 9 *A*). The fourth ventricle at these levels was almost completely filled with folia of the cerebellar vermis, and its dorsolateral angles were packed with the impacted tufts of choroid (fig. 11). Sections through the upper cervical segments revealed a syringomyelia-like cavity lying dorsal to the central canal (fig. 9 *B*). In focal areas this cavity was lined by ependymal glia, but for the most part it bordered directly on medullary substance. The relation of this cavity to the fourth ventricle is seen in figure 12, which is a schematic reconstruction of the hindbrain and cervical portion of the cord as seen in a midsagittal plane. In this figure, *F.M.* indicates the relation of the foramen magnum to the neuraxis. The brain was severed from the spinal cord at *C*. The fourth

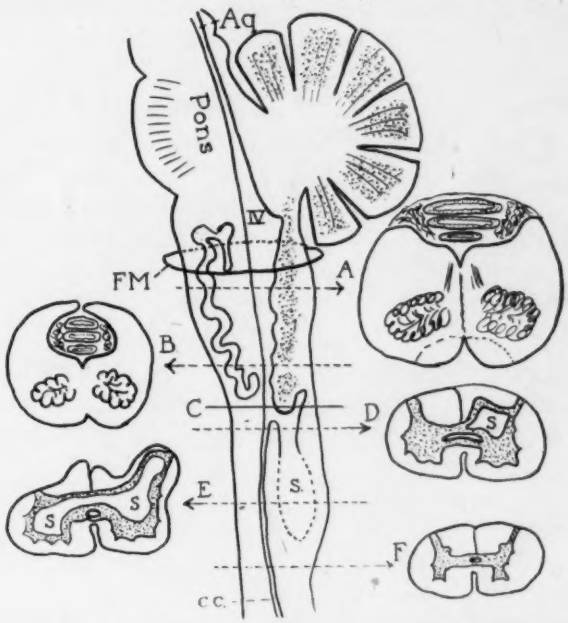

Fig. 12.—Schematic drawing of a midsagittal section through the hindbrain in case 3. *FM* indicates the foramen magnum, *IV*, the fourth ventricle, and *S*, the syrinx. Level *A* corresponds to that in figure 9 *A*, and level *E* to that in figure 9 *B*. The brain was severed from the spinal cord at *C* in figure 8.

ventricle was elongated downward and ended in a diverticulum-like outpouching in the dorsal half of the spinal cord. A portion of the inferior portion of the vermis was also pulled downward. In its lowermost portion the fourth ventricle was filled with tufts of choroid plexus.

Of special interest in this case are the deformity of the fourth ventricle and its diverticulum extending into the dorsal columns of the uppermost cervical levels of the spinal cord. Such deformitiy of the hind end of

the fourth ventricle was early described by Gudden [12] in a case of spina bifida. It became apparent from the study of my cases and of those in the literature that the downward migration of the hindbrain and the rostral migration of the spinal cord do not always occur on a uniform plane. Since in some cases only the dorsal portion of the spinal cord is fixed to its surroundings (fig. 2), the ventral, unfixed portion will ascend more than the fixed portion. As a result of this unequal ascent of the spinal cord, the dorsal portion of the hindbrain will necessarily move downward more than its ventral portion. In some instances this results in a peculiar deformity of the fourth ventricle, namely, a dorsal pocket, and in the presence of a nodule on the dorsum of the medulla. I believe that the cerebrospinal fluid secreted by the tufts of the choroid plexus impacted in the hind end of the fourth ventricle played a role in the dilatation of this portion of the ventricular system and that the syringomyelic-like cavity lying dorsal to the central canal in the uppermost cervical levels is either a simple diverticulum of the fourth ventricle from which the ependymal lining has fallen off or a syrinx resulting from the rupture of the cerebrospinal fluid through the ependyma and its spread along the path of least resistance through the dorsal columns of the spinal cord.

Just as the spinal dysraphic state may be manifested at several points along the spinal column, it may also be associated with homologous changes in the brain. Congenital atresia of the aqueduct of Sylvius may coexist with lumbosacral spina bifida, and the resulting hydrocephalus may not be a complication of the spinal dysraphic state but may rather be a direct result of a primary condition—the atresia of the iter.

COMMENT

From the study of my cases and a review of the literature, it is apparent that the distant neuroanatomic changes resulting from the spina bifida state are directly related to one factor, namely, the abnormal fixation of the spinal cord, its meninges or its roots. The degree and extent of the fixation will, of course, determine the time of onset and the degree of the neuroanatomic alterations. Since internal hydrocephalus, whether produced by stenosis of the aqueduct of Sylvius or by impaction of the hindbrain into the vertebral canal, is a striking complication of spina bifida, one notes a parallelism between the degree of dysraphism and the degree and time of onset of the hydrocephalus.

12. Gudden, H.: Ueber einen Fall von Knickung der Medulla oblongata und Teilung des Rückenmarks, Arch. f. Psychiat. **30**:866, 1898.

In cases of the ulcerative form of spina bifida it is not uncommon to observe hydrocephalus at birth. In cases of less severe deformity (pure meningocele) the hydrocephalus occurs later in life, is often of a far less severe degree or does not supervene at all.

The origin of the hydrocephalus in cases of spina bifida has led to much theorizing. Some believe that the hydrocephalus occurring in cases of spina bifida is communicating in type and results from a failure in the cleavage of the periencephalic mesenchyme and that the latter is a coincident anomaly which, like spina bifida, is also dependent on failure of normal cleavage. Penfield and Cone [13] have commented on the absorptive function of the sac and have stressed its preservation in the repair of the spina bifida. Many have commented on the fact that operation on the spina bifida often precipitates the onset of the hydrocephalus. Gross and Sachs [14] contended, however, that "hydrocephalus does not occur after operation as frequently as it has been supposed, though one can never tell beforehand in which case it may appear."

In many cases hydrocephalus exists before operation and goes unnoticed, as seen in the report of Shapiro and Tosti,[15] who studied 6 cases of spina bifida in which the head measurements were normal and there was no clinical suggestion of hydrocephalus. Ventriculograms, however, revealed marked dilatation of the ventricular system, particularly the lateral ventricles. In a study of the mechanism of internal hydrocephalus in cases of spina bifida, Russell and Donald [16] called attention to the Arnold-Chiari malformation, which they found in 10 successive cases of meningomyelocele. They stated that the Arnold-Chiari deformity may be the cause of the hydrocephalus which in some cases complicated meningocele, but they made no statement as to the probable mode of development of this deformity, adding, "If [the] hydrocephalus . . . were due to such a malformation [Arnold-Chiari], then air injected by the lumbar route would collect in the ventricles and not in the sulci upon the cerebral convexities." In several cases that came under my observation the spread of the suppuration took just this course. The spinal leptomeninges up to the level of constriction were densely infiltrated; the ventricular system was filled with pus

13. Penfield, W., and Cone, W. V.: Spina Bifida and Cranium Bifidum, J. A. M. A. **98**:454 (Feb. 6) 1932.

14. Gross, S. W., and Sachs, E.: Spina Bifida and Cranium Bifidum, Arch. Surg. **28**:874 (May) 1934.

15. Shapiro, B., and Tosti, V. G.: Ventricular Dilatation in Spina Bifida, J. Pediat. **16**:318, 1940.

16. Russell, D. S., and Donald, C.: The Mechanism of Internal Hydrocephalus in Spina Bifida, Brain **58**:203, 1935.

(pyocephalus), and the meninges over the cerebral convexities showed minimal inflammatory changes. Parker and McConnell [17] described 3 cases of internal hydrocephalus without spina bifida in which an Arnold-Chiari deformity of the brain was observed. In the first case, that of a youth 18 years of age with internal hydrocephalus and evidence of damage to the lower cranial nerves, a diagnosis of tumor of the foramen magnum was made. In the second case, that of a child 10 years of age, a diagnosis of medulloblastoma of the vermis cerebelli was made, and in the third, that of a patient in the fourth decade of life, the diagnosis of a lesion of the posterior fossa was decided on. The findings at operation in these 3 cases were strikingly similar and consisted of: (1) prolongation of the cerebellar tissue through the foramen magnum into the spinal canal, which extended to the second or third cervical segment; (2) caudal displacement of the medulla oblongata so that the closed portion of the medulla lay within the spinal canal; (3) direction of the upper cervical roots upward toward their respective intervertebral foramens rather than horizontally and (4) protrusion on the dorsum of the medulla, which on section was found to be just a distortion of the medulla. In these 3 cases there was no evidence of spina bifida, but roentgenograms of the spine were not taken to determine whether spina bifida occulta was present. In a discussion of the Parker-McConnell presentation, Dr. Henry Alsop Riley stated that he had heard Dorothy Russell's [16] presentation of similar material, and added: [17]

> It seemed to me that the most plausible explanation for this peculiar deformity is a failure of the normal ascent of the spinal cord within the vertebral canal by some process which shortens the filum terminale or immobilizes the cord in some other way, thus preventing the normal ascent of the lower end of the spinal cord to the first lumbar vertebra.

I believe that the Arnold-Chiari deformity is not a developmental defect but rather the result of downward migration of the hindbrain. In most instances this downward migration results from traction from below (due to the fixation of the spinal cord, its meninges and/or its roots). This downward migration also occurs in some instances of platybasia and brevicollis (Klippel-Feil syndrome), in which there may be no evidence of traction. Discussion of this subject, however, takes one too far afield from the title of this contribution and will be handled in detail elsewhere.

It should be emphasized that the fixation of the spinal cord may be unassociated with a bony defect and that a negative roentgenogram does not exclude the possibility of a dysraphic anomaly in the meninges or spinal cord which may result in its fixation. Of the roles in the

17. Parker, H. L., and McConnell, A. A.: Internal Hydrocephalus Resulting from a Peculiar Deformity of the Hindbrain, Tr. Am. Neurol. A. **63**:14, 1937.

development of hydrocephalus of the two deformities resulting from this fixation, namely, impaction of the hindbrain in the vertebral canal and stenosis of the aqueduct of Sylvius, I believe that of the latter is more important and that it has not been sufficiently emphasized. In a hydrodynamic system a slight narrowing of one of the passages may result in grave dilatation anterior to the stenosis. In most instances of hydrocephalus resulting from spina bifida the dilatation is restricted to the lateral and third ventricles, the aqueduct being narrow and the fourth ventricle not dilated. The stenosis of the aqueduct assumes a greater importance when one notes that atlanto-occipital decompression, to relieve the narrowing in the cerebrospinal fluid pathways resulting from the impaction of the hindbrain in the vertebral canal, does not necessarily preclude the continuing development of hydrocephalus in some cases.

Of late one notes renewed interest in platybasia.[18] This disorder, which is essentially a deformity of the base of the skull, frequently results in impingement on the brain stem and may be associated with syringomyelic symptoms. Since impaction of the hindbrain also occurs in the Arnold-Chiari deformity, it was not surprising to find hydromyelia in the upper cervical segments in some cases, or even a syringomyelic-like cavity (fig. 9 *B*). I must emphasize, however, that in my case at least the changes were not typical of true syringomyelia and that they resulted from increased spinal fluid pressure in the partially closed-off portion of the fourth ventricle. Pressure on the anterior spinal arteries near their origin and on the vertebral system of veins, due to the impaction of the hindbrain, also may play a role in the changes in the cerebellum and the spinal cord.

In some cases the impaction of the hindbrain results in pressure on the lower cranial nerves, as in the case of Penfield and Coburn,[19] in which the patient, 29 years of age at the time of death, was operated on at the age of 3 for spina bifida and meningocele. She did well until the age of 16, when difficulty in hearing developed. The loss of hearing advanced slowly and did not become important until the age of 27. When 26 years old she noticed that her right eye watered more than normally and her friends told her that there was weakness of the right side of her face. At necropsy the seventh, eighth, ninth and tenth cranial nerves were thin and elongated. In the first case of Parker and McConnell,[17] that of a youth of 18 years of age with internal hydrocephalus and evidence of damage to the lower cranial nerves, a similar condition was found at operation.

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18. Gustafson, W. A., and Oldberg, E.: Neurologic Significance of Platybasia, Arch. Neurol. & Psychiat. **44**:1184 (Dec.) 1940.

19. Penfield, W., and Coburn, D. F.: Arnold-Chiari Malformation and Its Operative Treatment, Arch. Neurol. & Psychiat. **40**:328 (Aug.) 1938.

The clinical significance of a short cauda equina is little except that it indicates a low-lying conus which may be injured by spinal puncture. Since my patients were all under 1 year of age, I can do no more than comment on Katzenstein's [5] theory that the elongation of the spinal cord between the site of fixation and the medulla may result later in life in symptoms referable to the spinal cord.

CONCLUSIONS

In many instances of spina bifida (spinal dysraphism) there is abnormal fixation of the spinal cord which precludes its adequate rostral migration with continued development. This abnormal fixation in some cases results in a pleomorphic variety of neuroanatomic alterations in distant parts of the nervous system. These alterations are:

1. Short cauda equina and low-lying conus medullaris.
2. Abnormal stretching of the spinal cord above the site of fixation.
3. Elongation of the hindbrain, with localization in the vertebral canal of the medulla oblongata, the choroid plexus of the fourth ventricle and parts of the cerebellum.
4. Dysplasia of some of the cerebellar folia.
5. Elongation of the lowermost cranial nerves with their compression at the foramen magnum by the impaction of the hindbrain.
6. Stenosis of the aqueduct of Sylvius.
7. Internal hydrocephalus due to stenosis of the aqueduct of Sylvius and to impaction of the hindbrain in the foramen magnum.
8. Deformity of the medulla oblongata and of the hind end of the fourth ventricle.
9. Hydromyelia of the uppermost cervical levels of the spinal cord.
10. Syringomyelic-like cavitation in the cervical portion of the spinal cord.
11. Pressure on the anterior spinal arteries and the vertebral system of veins at the foramen magnum.

PYRUVIC ACID STUDIES IN THE WERNICKE SYNDROME

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In 1881 Wernicke,[1] on the basis of 3 patients studied during life and at the autopsy table, delineated a clinical syndrome characterized by clouding of consciousness, varying ophthalmoplegias and ataxia. The author did not indict alcohol as the causative agent, but suggested that various toxins, including alcohol, might produce the clinicopathologic picture of acute hemorrhagic polioencephalitis superior. The essential pathology was described by Wernicke and has been further elaborated by others.[2] In general, the lesions are confined to the periventricular gray matter and are characterized by small foci of degeneration and varicose deformities of the blood vessels. There is subacute necrosis of the adjoining parenchyma, and small petechial hemorrhages are frequently, but not always, seen throughout the lesions. The areas most constantly involved are the paramedian and paraventricular nuclei of the thalamus and the hypothalamus, the mamillary bodies and the

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1. Wernicke, C.: Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende, Berlin, T. Fischer, 1882, vol. 2, p. 229.

2. (*a*) Hunt, J. R.: A Contribution to Our Knowledge of the Polioencephalitis Superior (Wernicke Type), New York M. J. **83**:289, 1906. (*b*) Gamper, E.: Zur Frage der Polioencephalitis haemorrhagica der chronischen Alkoholiker, Deutsche Ztschr. f. Nervenh. **102**:122, 1928. (*c*) Bender, L., and Schilder, P.: Encephalopathia Alcoholica (Polioencephalitis Haemorrhagica Superior of Wernicke), Arch. Neurol. & Psychiat. **29**:990 (May) 1933. (*d*) Alexander, L.: Wernicke's Disease, Am. J. Path. **16**:61, 1940.

periaqueductal regions of the midbrain (nuclei of the third and fourth nerves), the nucleus of the abducens nerve, the nucleus triangularis and Bechterew's nucleus and the dorsal nucleus of the vagus nerve.

Most cases reported subsequent to Wernicke's original report were those of inebriates, and alcoholism gradually came to be accepted as the etiologic basis of this condition. On the other hand, a review of the literature reveals many instances of this syndrome in nonalcoholic persons.[3] Many authors suggested that alcohol was only indirectly responsible for the syndrome, but it remained for Alexander and his co-workers to show that the lesions of Wernicke's polioencephalopathy occurring in man and the lesions of the disease which he and his co-workers produced in thiamine-deficient pigeons,[4] foxes and fish [5] were identical in their topographic distribution and in their morphologic and histologic characteristics.

We have recently studied 34 clinical cases which tend to confirm this thesis. Of the total number of patients, 3 were nonalcoholic (2 were depressed and refused to eat and 1 suffered from pulmonary tuberculosis with associated vomiting) and the other 31 were chronically alcoholic. The cases of 27 of these patients have been reported in detail elsewhere.[6] The results to date of our clinical studies [7] may be summarized as follows:

The syndrome as originally described by Wernicke is probably a combination of several nutritional deficiencies, any one of which may

3. Ohkuma, T.: Zur pathologischen Anatomie des chronischen Alkoholismus, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:94, 1930. Tanaka, I.: So-Called Breast Milk Intoxication, Am. J. Dis. Child. **47**:1286 (June) 1934. Neubürger, K.: Ueber die nichtalkoholische Wernicksche Krankheit, insbesondere über ihr Vorkommen beim Krebsleiden, Virchows Arch. f. path. Anat. **298**:68, 1936; Wernicksche Krankheit bei chronischer Gastritis, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:208, 1937. Környey, S.: Wernicke-Korsakow-Prozess als Komplikation bösartiger extraneuraler Geschwülste, Deutsche Ztschr. f. Nervenh. **144**: 241, 1937. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy: Its Alcoholic and Non-Alcoholic Incidence, J. Path. & Bact. **48**:245, 1939. Ecker, A. D., and Woltman, H. W.: Is Nutritional Deficiency Basis of Wernicke's Disease? Report of Case, J. A. M. A. **112**:1794 (May 6) 1939. Wernicke.[1] Alexander.[2d]

4. Alexander, L.; Pijoan, M., and Meyerson, A.: Beri-Beri and Scurvy, Tr. Am. Neurol. A. **64**:135, 1938.

5. Alexander, L.; Green, R. G.; Evans, C. A., and Wolf, L. E.: Alcoholic Encephalopathy in Man and Fish-Diet Disease in Foxes and Fishes, Tr. Am. Neurol. A., 1941, to be published.

6. Jolliffe, N.; Wortis, H., and Fein, H. D.: The Wernicke Syndrome, Arch. Neurol. & Psychiat. **46**:569 (Oct.) 1941.

7. Wortis, H., and Jolliffe, N.: The Present Status of Vitamins in Nervous Health and Disease, New York State J. Med. **41**:1461, 1941. Jolliffe, N., and

be predominant. Delirium, with its marked increase in psychomotor activity and hence in total metabolism, usually precedes the development of this syndrome. It is believed that this increases certain of the vitamin requirements of the patient and tends to aggravate any latent deficiency state which may be present. Other deficiency syndromes, such as pellagra, nicotinic acid deficiency encephalopathy, ariboflavinosis, and scurvy, may and do superimpose themselves on or accompany the Wernicke syndrome. These require specific treatment. The ophthalmoplegia responds to thiamine therapy but not to administration of nicotinic acid, riboflavin or pyridoxine. The ophthalmoplegia is invariably preceded or accompanied by acute peripheral symmetric polyneuropathy. Since the latter is almost always associated with thiamine deficiency, this observation supports Alexander's thesis that the two disturbances have a common cause and that the polioencephalopathic changes represent a more complete deficiency of thiamine. In most cases the clouding of consciousness responds to treatment with thiamine hydrochloride, but in other cases it may be related to any other factor which interferes with proper brain metabolism, such as lack of carbohydrate, oxygen, nicotinic acid or riboflavin, and possibly to lack of other substances, now under investigation. The ataxia is difficult to evaluate both as to its genesis and as to its response to therapy. All patients who received adequate vitamin therapy recovered unless a complicating condition was present which in itself was sufficient cause for death. We have now had 14 consecutive recoveries among patients so treated. In the recovered patients the succession of a Korsakoff syndrome is the rule. The latter does not show a consistent response to thiamine therapy, as has frequently been claimed.[7a]

Wortis, H.: Encephalopathia Alcoholica, Am. J. Psychiat., to be published. Jolliffe, N.; Bowman, K. M.; Rosenblum, L. A., and Fein, H. D.: Nicotinic Acid Deficiency Encephalopathy, J. A. M. A. **114**:307 (Jan. 27) 1940. Jolliffe, N., and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict, ibid. **107**:642 (Aug. 29) 1936. Goodhart, R. S., and Jolliffe, N.: Effects of Vitamin B (B_1) Therapy on the Polyneuritis of Alcohol Addicts, ibid. **110**:414 (Feb. 5) 1938. Wortis, H.; Bueding, E., and Jolliffe, N.: Pyruvic Acid Studies in the Peripheral Neuropathy of Alcohol Addicts, New England J. Med., to be published. Wortis, H.: Delirium Tremens, Quart. J. Stud. Alcohol **1**:251, 1940. Bowman, K. M.; Wortis, H., and Keiser, S.: The Treatment of Delirium Tremens, J. A. M. A. **112**:1217 (April 1) 1939. Jolliffe, N.; Wortis, H., and Stein, M. H.: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism, Quart. J. Stud. Alcohol **2**:73, 1941.

7a. Weiss, S., in Cecil, R. L.: Textbook of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1938, p. 562. Brodsky, N.: Treatment of Alcoholic Psychoses with Thiamin Chloride, J. Connecticut M. Soc. **2**:228, 1938.

It is known that the brain depends for its normal functioning essentially on a carbohydrate substrate, an adequate supply of oxygen and various enzyme and coenzyme systems. It has previously been shown that thiamine pyrophosphate is necessary for the in vitro catabolism of pyruvic acid.[8] That this mechanism also operates in human beings is suggested by the fact that in oriental beriberi [9] and the peripheral symmetric polyneuropathy of alcohol addicts [10] (diseases associated with a deficiency of thiamine) hyperpyruvemia has been observed. We have furthermore studied 280 patients with various neuropsychiatric and medical disorders unassociated with any clinical evidence of thiamine deficiency, and all of these showed normal levels of pyruvic acid in the blood.[11]

We [12] have previously reported that the normal fasting pyruvic acid content of the blood ranged from 0.77 to 1.17 mg. per hundred cubic centimeters (average, 0.98 mg.), and we have considered as abnormally high any fasting level of pyruvate above 1.30 mg. per hundred cubic centimeters of blood. Pyruvic acid is a keto acid and therefore a bisulfite-binding substance, but the total value for bisulfite-binding substances cannot be used as an accurate indication of the pyruvic acid level of any sample.[13]

Pyruvic acid is also a normal intermediary of carbohydrate catabolism in man.[14] In 27 normal persons the blood pyruvate was significantly elevated after the ingestion of dextrose (1.75 Gm. per kilogram of body weight) and returned to the fasting level within three hours.

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8. Banga, I.; Ochoa, S., and Peters, R. A.: Pyruvate Oxidation in Brain: Some Dialyzable Components of Pyruvate Oxidation System, Biochem. J. **33**:1980, 1939.

9. Lu, G. D.: Studies on Metabolism of Pyruvic Acid in Normal and Vitamin B_1 Deficient States, Biochem. J. **33**:774, 1939.

10. Wortis, H., and Bueding, E.: Clinical Significance of Pyruvic Acid Content of the Blood and Cerebrospinal Fluid, Tr. Am. Neurol. A. **66**:90, 1940.

11. Bueding, E.; Wortis, H.; Stein, M. H., and Jolliffe, N.: Pathological Variations in Blood Pyruvic Acid, J. Clin. Investigation **20**:441, 1941.

12. Bueding, E., and Wortis, H.: Stabilization and Determination of Pyruvic Acid in the Blood, J. Biol. Chem. **133**:585, 1940.

13. Wortis, H.; Bueding, E., and Wilson, W. E.: Bisulfite Binding Substances in the Blood and Cerebrospinal Fluid, Proc. Soc. Exper. Biol. & Med. **43**:279, 1940; The Clinical Significance of Bisulfite Binding Substances in the Blood and Cerebrospinal Fluid, Am. J. Psychiat. **97**:573, 1940.

14. Bueding, E.; Stein, M. H., and Wortis, H.: The Formation of Pyruvic Acid Following Glucose Ingestion in Man, J. Biol. Chem. **139**:793, 1941.

The maximum rise was usually observed at the end of the first hour [15] (chart 1).

The present study was undertaken to determine whether or not the Wernicke syndrome was associated with a disturbance in pyruvic acid metabolism.

MATERIALS AND METHODS

Eleven patients with Wernicke's disease were studied. Determinations were made on patients while fasting and at rest in bed. In 7 of these subjects the blood pyruvate was followed for four hours after the ingestion of 1.75 Gm. of dextrose per kilogram of body weight. Pyruvic acid determinations were made by the method of Bueding and Wortis,[12] with the modifications subsequently published.[15]

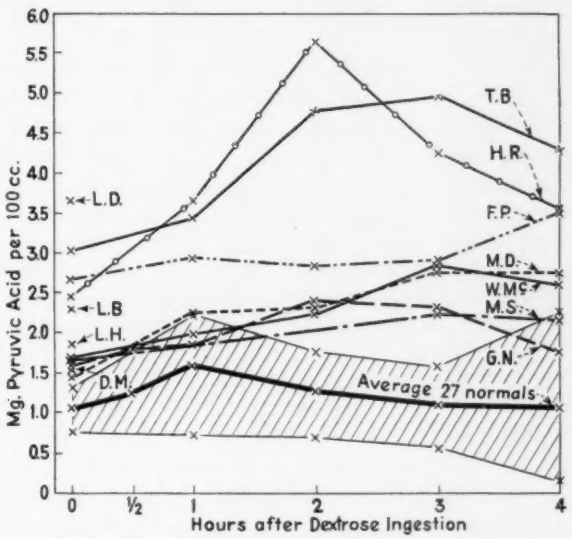

Chart 1.—Pyruvate curves following ingestion of dextrose in normal persons and in patients with the Wernicke syndrome. The shaded area represents three times the standard deviation of each point on the average curve for 27 normal subjects.

RESULTS (CHARTS 1, 2 AND 3)

In 11 patients with Wernicke's syndrome, the fasting level of pyruvate in the blood was invariably elevated. The figures ranged from 1.44 to 3.63 mg. per hundred centimeters (average 2.17 mg.). Of even greater significance is the fact that when 7 of these patients were subjected to the additional stress of metabolizing ingested dextrose the maximum rise in blood pyruvate was not only greater than that seen in

15. Bueding, E.; Stein, M. H., and Wortis, H.: Blood Pyruvate Curves Following Glucose Ingestion in Normal and Thiamine-Deficient Subjects, J. Biol. Chem. **140**:697, 1941.

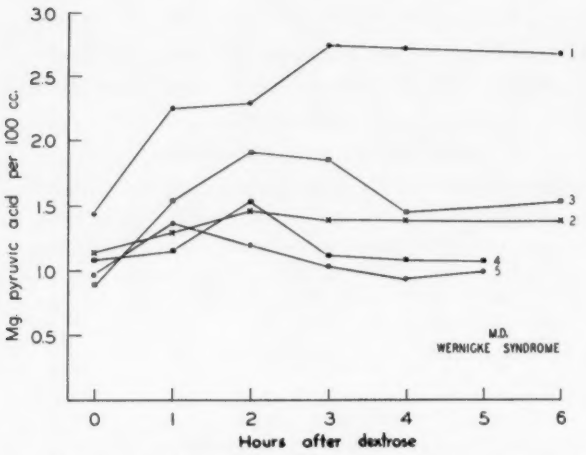

Chart 2.—Effects of therapy on the pyruvate curve of a patient with the Wernicke syndrome after ingestion of dextrose.

Curve *1* was obtained on admission; curve *2*, after administration of a basal diet plus thiamine hydrochloride (100 mg. given once a day intramuscularly) for three days; curve *3*, after eighteen days of this therapy; curve *4*, after administration of a basal diet plus thiamine hydrochloride (100 mg. once a day) for twenty-two days and nicotinic acid (1,000 mg. once a day) for four days, and curve *5*, after thirteen additional days of the therapy indicated for curve *4*.

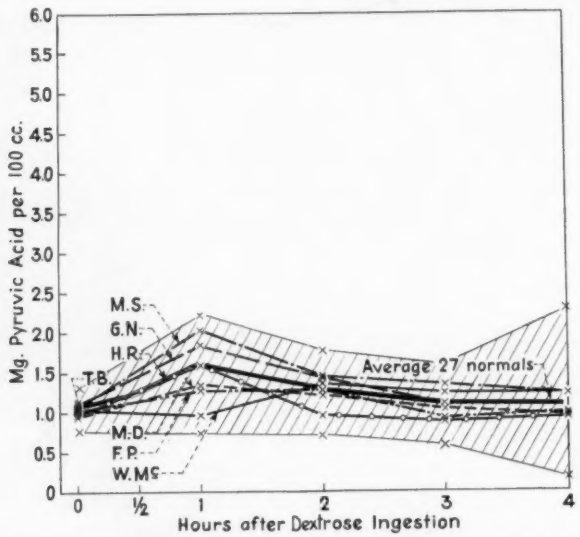

Chart 3.—Pyruvic acid metabolism in patients with Wernicke's disease following therapy with thiamine and other members of the vitamin B complex. The shaded area represents three times the standard deviation of each point on the average curve for 27 normal subjects.

normal subjects, but the elevation above the fasting level was maintained for at least four to five hours. It should be further noted that in these subjects the maximum increase did not occur at the end of the first hour, as seen in the normal subjects, but the pyruvate continued to rise and maximum values were found at the end of the second, third or fourth hour.

After vitamin B therapy, the fasting level of blood pyruvate rapidly returned to normal, but the pyruvic acid curve following ingestion of dextrose returned to normal levels only after prolonged treatment. The clinical improvement (disappearance of ophthalmoplegia and improvement in the mental status) occurred in twenty-four to seventy-two hours and always antedated the complete return of pyruvate metabolism to normal. On the other hand, the clinical improvement was always associated with marked reduction in the fasting level of pyruvic acid in the blood. A typical response to therapy is indicated in chart 2. This chart characterizes fairly well the response to therapy in all the cases studied. The final curves obtained after prolonged treatment in 6 of these cases are noted in chart 3.

COMMENT

The results of our clinical and chemical studies together with the previously reported pathologic observations of Alexander,[16] lead us to conclude that the Wernicke syndrome is constantly associated with a disturbance in pyruvic acid metabolism. Thiamine therapy reverses the ophthalmoplegia and usually improves the mental status. These facts justify the assumption that the Wernicke syndrome is invariably associated with a thiamine deficiency. We wish, however, to reemphasize the fact that the Wernicke syndrome, as we see it clinically, does not represent a simple thiamine deficiency. In our experience, it is regularly associated with a deficiency in thiamine, but there is usually an additional lack of other nutritive essentials. In the treatment of patients with this syndrome, we therefore advocate a high calory, vitamin-rich diet, with other vitamin concentrates in addition to thiamine. In the absence of complications sufficient in themselves to cause death, we have had no fatality in any case in which this treatment was employed.

SUMMARY

Patients with the Wernicke syndrome show inability to metabolize pyruvic acid properly.

16. Alexander.[2d] Alexander, Pijoan and Meyerson.[4] Alexander, Green, Evans and Wolf.[5]

After prolonged treatment with thiamine hydrochloride and with thiamine hydrocloride plus other members of the vitamin B complex, this defect in pyruvic acid metabolism is corrected. This is associated with disappearance of the ophthalmoplegia and improvement in the mental status.

Our clinical and chemical observations, together with the pathologic changes previously reported by Alexander and his co-workers, demonstrate that the Wernicke syndrome is invariably associated with a deficiency of thiamine.

INDUCTION OF METRAZOL CONVULSIONS WITH THE PATIENT UNDER NITROUS OXIDE ANESTHESIA

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It is common knowledge that apprehension, fear and panic are frequent accompaniments of metrazol shock therapy. This fear is produced by a series of subjective sensations experienced by the patient in the interval between the injection of the drug and the onset of the convulsion. Patients complain variously, stating that the sensation may simulate crushing of the chest, electrocution, bursting open of the head or impending death.[1] These profound fear reactions produce a marked and understandable resistiveness in the patient, which is commonly of such degree that treatment must be suspended prematurely. An attempt to alleviate this resistiveness arising from severe fear reactions in the following 2 cases prompted me to induce metrazol convulsions with the patient under anesthesia.

A white man aged 56, a machinist, who was suffering from severe and incapacitating melancholia of two years' standing, entered the Good Samaritan Hospital in Cincinnati on Nov. 5, 1939 for metrazol convulsive therapy. Two successful convulsions were produced at three day intervals, and the patient showed definite objective improvement. His fear reaction, however, was so great that he refused unconditionally to undergo further treatment. On his knees he implored to be taken home, or even killed, rather than be subjected to another injection of metrazol. It was determined to attempt further injections with the patient under nitrous oxide anesthesia. The procedure was found to be practicable, and after four more convulsions, induced while under anesthesia, the patient recovered and has been at work steadily since December 1939.

From the Department of Physiology, University of Cincinnati College of Medicine.

Read before the Section on Nervous and Mental Diseases at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 6, 1941.

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A second patient, a white man aged 59, a gambler, was treated for melancholia with five metrazol shocks in 1938. Treatment was terminated because of marked resistiveness on his part, although he was discharged as improved. Symptoms recurred in April 1940, and he refused to submit to further metrazol therapy because of the disturbing subjective sensations which had accompanied previous administrations of the drug. With nitrous oxide anesthesia, however, five more shocks were given at three day intervals, without causing any fear or resistiveness. The patient has been relieved of his symptoms for more than a year.

These two clinical experiences, and an independent report by two English observers, Neustatter and Freeman,[2] who found that metrazol shock therapy was feasible when carried out under either nitrous oxide or cyclopropane anesthesia, prompted a wider use of the method. This report concerns itself with 323 metrazol shocks induced in 40 patients while under nitrous oxide anesthesia.

TECHNIC

The patient is placed in bed in the usual position of spinal hyperextension. The inhalation is begun with the Heidbrink or other suitable apparatus, using a mixture of 88 per cent nitrous oxide and 12 per cent oxygen. When the corneal reflex is lost (and this requires roughly one minute of inhalation) the needle is introduced into the patient's vein. The mask is then removed while the metrazol is injected quickly. At first it was thought advisable to open the direct flow oxygen valve of the apparatus and allow the patient two inhalations of 100 per cent oxygen just before removing the mask, but later observations have shown this to be superfluous and it has been abandoned.

THE FIT

In all 323 instances, the preconvulsive period, the period of the fit, the pattern of the fit and the postconvulsive period of recovery have been entirely similar to those one might expect in a series of metrazol shocks induced in conscious patients.

The preconvulsive, or latent, period between the time of injection of the drug and the onset of convulsive movements was timed by an observer at the bedside. This was found to vary between four and thirty seconds, with an average of eleven and two-tenths seconds (fig. 1). The duration of the fit, timed in the same manner, was found to vary between twenty-five and seventy-five seconds, with an average of forty-four and four-tenths seconds (fig. 2). These intervals are similar to those encountered in metrazol convulsions induced in conscious

2. Neustatter, W. L., and Freeman, H.: The Prevention of Fear in Cardiazol Therapy, Lancet **2**:1071 (Nov. 18) 1939.

patients. No attempt was made to record the time required for the recovery of consciousness following the fit, but it may be said that the usual variability was found here. Some patients were fully recovered

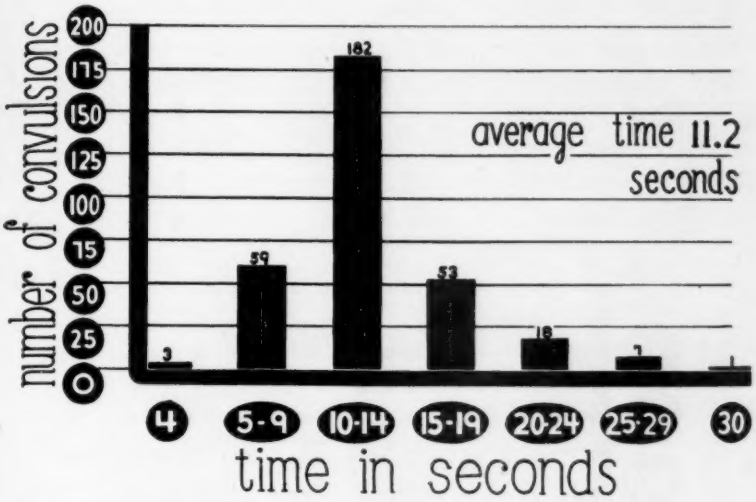

Fig. 1.—Latent period between injection of metrazol and onset of fit in 323 effective convulsions induced with the patient under gas anesthesia.

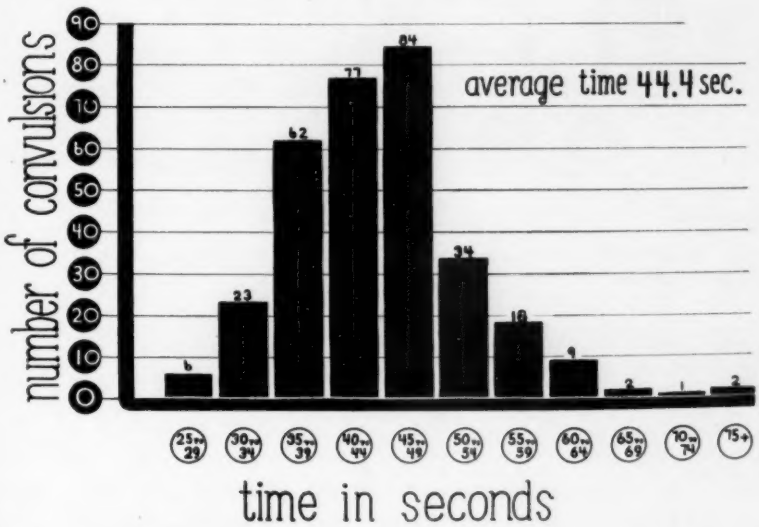

Fig. 2.—Duration of 323 effective convulsions induced with the patient under gas anesthesia.

and reoriented in four or five minutes, whereas others remained confused, restless and disoriented for an hour or more. The pattern of the fit, with individual variations, was characterized by the same violent

initial tonic flexion, initial grunt and ensuing clonic movements seen in the orthodox metrazol convulsion.

DOSAGE

The dosage of metrazol used in induction of 323 fits with the patient under gas anesthesia varied from 4.5 to 15 cc., with an average of 9.4 cc. (fig. 3). This is probably a higher average dose than would be employed in a similar series of conscious patients. Some of this increase may be explained as a tendency toward the arbitrary use of high doses on my part. Three hundred and fifty-six attempts to induce convulsions

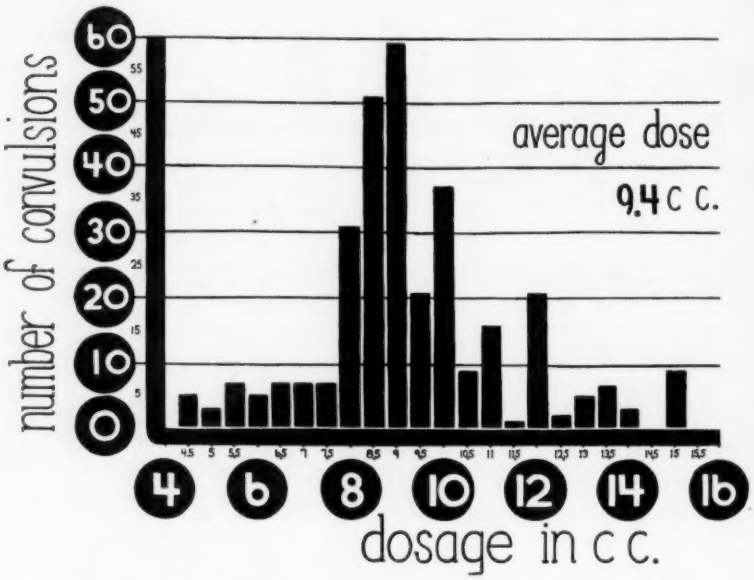

Fig. 3.—Dosage of metrazol used in 323 effective convulsions induced with the patient under gas anesthesia.

resulted in 33 failures and 323 successes. The small percentage (9.26) of subconvulsive reactions, or failures, probably indicates that I have chosen relatively high doses arbitrarily.

An experiment in dosage requirements was unwittingly performed for us by the second patient aforementioned. A comparison of the doses employed to induce fits in this patient while he was conscious, in 1938, and those employed while he was under nitrous oxide anesthesia, in 1940, discloses that in the first instance an average dose of 7.54 cc. was inadequate in that it produced 2 failures in 7 attempts whereas in the

second instance, with gas anesthesia, an average dose of 9.20 cc. produced no failures in 5 attempts. This comparison is shown graphically in figure 4. This leads one to suspect that no profound increase in dosage is necessary when metrazol convulsions are induced under nitrous oxide anesthesia.

A necessity to increase the dose slightly as treatment progressed was found in 29 of the 40 cases. This is consistent with the experience in metrazol shock therapy of unanesthetized patients.

COMPLICATIONS

Multiple convulsions occurred three times in the series of 323 shocks. In 1 instance five convulsions occurred within two hours; in a second

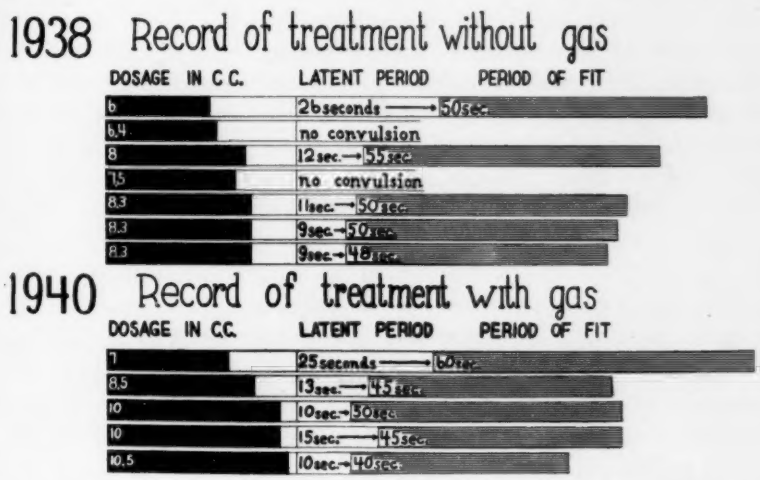

Fig. 4.—Record of A. H., a white man aged 60, a gambler, with melancholia.

four convulsions occurred within one and a half hours, and in a third a second convulsion followed twenty minutes after the first. On each occasion a second injection of the drug had been made because a portion of the first injection had been deposited extravenously in the soft tissues. Multiple convulsions did not occur after single injections of metrazol and are apparently no more to be expected than they are in unanesthetized patients.

Two patients abandoned therapy because they objected to the anesthetic. The first was a miserably unhappy patient with agitated melancholia of four years' duration who had been uncooperative throughout his illness. The second was a woman from the Kentucky hills with misophobia and a hand-washing obsession who was frightened by the hospital atmosphere as well.

Routine roentgenographic study of the dorsal portion of the spine was made on all patients. The plates were read by Drs. W. M. Doughty,

E. R. Bader and H. G. Reineke. Compression fractures of the dosal part of the vertebal column were found in only 2 cases. In 1 of these cases metrazol had previously been given without gas anesthesia and the compression may have developed before the patient underwent the second form of therapy. There were no fractures of long bones, no dislocations and no muscle injuries. This low incidence of traumatic complications (5 per cent) is noteworthy when compared with the earlier frequency of 43 to 51 per cent.[3] In addition to careful restraint and spinal hyperextension, the use of anesthesia probably contributed to the small number of these injuries. Under gas anesthesia the patient is relaxed, and the assistants at the bedside have ample time to take all necessary precaution to insure proper restraint during the convulsion. In addition, the initial flexion movement of the fit appears to be less violent in patients under gas anesthesia.

Two of the patients have had recurrence of symptoms and have required further treatment after a period of improvement. Most of the patients have been treated within the last year, however, and it is not unlikely that more patients in the series may relapse later.

RESULTS OF THERAPY

None of these patients had been probated, and all were treated voluntarily in private hospitals. Of the 4 patients with schizophrenia who have recovered to the extent that they have resumed their former duties, 3 had shown symptoms for less than six months. The patients with melancholia presented a wide variation in duration and severity of symptoms, affording a representative group of cases. Eighteen patients had manic-depressive psychosis, depressed type, while the condition of 11 seemed to fall into the classification of involutional melancholia. The therapeutic results may be tabulated as follows:

Diagnosis	Recovered; Returned to Work	Improved; Not at Work	Unimproved	Abandoned Treatment	Total No. of Patients
Melancholia	20 (69%)	6 (21%)	2 (7%)	1 (3%)	29
Schizophrenia	4 (45%)	3 (33%)	2 (22%)	0	9
Obsessive-compulsive neurosis	0	1 (50%)	0	1 (50%)	2
					40

COMMENT

None of these patients complained of any fear reaction beyond that which is incident to the induction of nitrous oxide anesthesia. The typical "metrazol fear" was abolished. A much better rapport was established between patient and physician, so that further psychotherapy, when indicated, could be carried out without resistiveness born of fear

3. Polatin, P.; Friedman, M. M., and Harris, M. H.: Vertebral Fractures Produced by Metrazol-Induced Convulsions, J. A. M. A. **112**:1684 (April 29) 1939.

of metrazol injection. Eight of these patients, as they improved, were able to leave the hospital and return periodically for injections as ambulatory patients, and they did so without reluctance.

A further advantage of this technic is that the patient can be kept under light anesthesia for some minutes if a subconvulsive dose of metrazol is given, and a second larger dose can then be given without waking the patient. In this way fear-provoking subconvulsive subjective sensations can be avoided.

It has been held by some observers [4] that the subjective experience of fear is the means whereby metrazol exerts its therapeutic effect; that is, the patient is literally frightened out of his psychosis. Meduna and Friedman [5] stated that "it is not altogether excluded that this very anxiety and fear might possibly be just as important as the other phases of the convulsion."

On the other hand, Cook [6] in a statistical study of 275 cases, found that there was a general tendency for greater therapeutic success to attend treatment of those patients who showed little or no fear. Cohen [7] produced fear reactions in a series of patients with subconvulsive doses of metrazol and obtained no therapeutic success. The patients were then benefited by metrazol in convulsive doses. Recent experience of workers with electrically induced convulsions indicates that although fear is absent in patients receiving such treatment, results are comparable to those in other forms of convulsive therapy. Fear has been reduced in metrazol convulsive therapy by premedication with insulin,[8] morphine [9] and scopolamine [10] without loss of therapeutic effectiveness. This study adds further direct proof for the contention that fear plays no role in the therapeutic effectiveness of metrazol convulsive therapy.

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5. Meduna, L. V., and Friedman, E.: The Convulsive-Irritative Therapy of the Psychoses, J. A. M. A. **112**:501 (Feb. 11) 1939.

6. Cook, L. C.: Has Fear Any Therapeutic Significance in Convulsion Therapy? J. Ment. Sc. **86**:484 (May) 1940.

7. Cohen, L. H.: Therapeutic Significance of Fear in Metrazol Treatment of Schizophrenia, Am. J. Psychiat. **95**:1349 (May) 1939.

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9. Hauser, A.: Experiences with Convulsive Shock Therapy, M. Rec. & Ann. **34**:464 (April) 1940.

10. Edlin, J. V., and Klein, E. S.: An Improvement in Convulsive Therapy with Metrazol by Premedication with Scopolamine Hydrobromide, Am. J. Psychiat. **97**:358 (Sept.) 1940.

SUMMARY AND CONCLUSIONS

Three hundred and twenty-three metrazol injections were made into 40 patients under nitrous oxide anesthesia.

This method was found to avoid the fear reaction so common in metrazol shock therapy without altering the convulsive pattern or the duration of the convulsion.

Little or no increase in the dose of metrazol was necessary to produce convulsions when the patient was under anesthesia.

Traumatic complications were minimized with this method (5 per cent), and it is suggested that anesthetizing the patient may be an aid in their avoidance.

Therapeutic results in cases of melancholia and schizophrenia were comparable to those obtained by orthodox metrazol therapy.

The method adds further direct proof for the contention that fear plays no role in metrazol convulsive therapy.

The technic is offered as a simple means of improving rapport and diminishing resistiveness in patients undergoing this therapy.

ABSTRACT OF DISCUSSION

DR. PHILIP E. PIKER, Cincinnati: I have had the opportunity of observing Dr. Fabing's employment of his procedure on a number of occasions and of using the technic on some of my patients. It has seemed satisfactory, not only for the reasons he has cited but in some other respects as well. Many a patient is excessively impressed by the number of assistants who march into his room behind the physician and stand ready to pounce on one or another part of his anatomy just preliminary to the onset of the convulsion. With Dr. Fabing's method only the anesthetist need accompany the doctor. Furthermore, with the first impact of the metrazol reaction occurring while the patient is still conscious, the few sceonds of preconvulsive fright make for physical agitation which might mitigate against his being able to so fix his position as to counteract most effectively the important initial flexion. This possibility is obviated in the case of the anesthetized patient.

I hesitate to speculate regarding Dr. Fabing's contention that the elimination of fear is a possible complement of successful convulsion therapy. It does seem likely that, except in so far as the patient may be apprehensive regarding the anesthetic itself, the element of conscious fear has been excluded by this technic. Nevertheless, the patient is aware that he is giving up his hold on consciousness and his contact with reality, and it is difficult to understand how this can do other than run afoul of the instinctual need for self preservation in some fashion. Furthermore, though the patient's consciousness has been blotted out by the anesthetic, there is no assurance that unconscious awareness and reactivity are in similar abeyance. Sleeping persons have been known to receive and react to external stimuli. It seems possible that an anesthetized person might develop an emotional response to a stimulus sufficiently overwhelming to make for practical decerebration. In this connection it has been of interest to me to note that immediately preceding the convulsion the anesthetized patient's face undergoes the same apprehensive grimace as does that of the conscious patient, though perhaps to a lesser degree.

The advent and acceptance of shock therapy have transformed many of us from cautious clinicians into intrepid adventurers into the realm of human welfare. We have received sanction for the use of a maneuver which is concrete and spectacular. I do not disparage shock treatment. Properly used in carefully selected cases, it undoubtedly has proved itself of value, not only as a therapeutic implement but as a stimulus to more interested and active research into nervous and mental disorders. To be deplored, however, is the unleashing of the "what do we have to lose" attitude—the rationalization that "anything goes" now, based on the two specious assumptions, first, that we have been given "the green light" regardless of individual consequences, and, second, that anything we accomplish is pure gain, since psychiatric therapy was nonexistent before the introduction of shock treatment.

There is the danger, in this situation, of becoming careless regarding the needs and welfare of the individual patient. Already we have adjusted our attitudes so that we produce profound disturbances in consciousness with relative impunity. In the technic which Dr. Fabing has described—and which I approve as safe and effective—the patient is put into coma by way of preparation for being put into coma. In yesterday's panel on prefrontal lobotomy, a procedure which undoubtedly is worthy of further investigation, the endorsers of the technic seemed agreed that even the best results involved some degree of depreciation in the total personality. If this is true, it is difficult to justify the procedure except in those cases in which prognosis is otherwise practically hopeless—cases in which there is truly nothing to lose and in which any gain is worth attempting. Yet we heard yesterday of instances in which lobotomy was performed after an illness of only a few months—certainly not sufficiently long to justify a therapeutic compromise such as this technic represents. This exemplifies the danger to which I refer, and which we dare not forget lest it prove so expensive to human life and integrity of personality that it act as a boomerang that may well nullify the promise of therapeutic progress held out in recent years.

DR. A. E. BENNETT, Omaha: I think it can now be stated that regular metrazol convulsive therapy is no longer warranted. It is unjustified because it is unsafe, and it has therefore been generally abandoned by careful therapeutists. Dr. Fabing is to be congratulated on his effort to modify the therapy. The problem of fear associated with the treatment is another valid objection to straight metrazol therapy. The fear accompanying the aura of metrazol convulsion is, I am sure, eliminated by Dr. Fabing's technic of preliminary nitrous oxide anesthesia. This initial fear is also alleviated by preliminary administration of scopolamine and is totally abolished by preliminary insulin coma.

There is another type of apprehension which results from any form of convulsive shock therapy, namely, the post-treatment confusional state. I wonder whether that element of fear is removed by this technic; it certainly is not entirely removed from other modifications of convulsive shock therapy. In my experience it shows up with all forms of such treatment after the third to the fifth induced shock and greatly concerns the patient. I believe it is the lesser of the two types of fear caused by the therapy. There is no doubt that elmination of fear is an improvement in therapy, and it does not interfere with effectiveness.

Dr. Fabing suggests that traumatic complications are minimized by his modification. I doubt if his experience is great enough to justify this conclusion. My associates and I administered 800 straight metrazol convulsions before we had the first fracture of an extremity; then we had a number. In our experience no

method of preliminary coma, orthopedic restraint or even spinal anesthesia has eliminated these complications. Only preliminary curarization sufficient to soften greatly the severity of the seizure can adequately prevent all traumatic complications of any form of convulsive shock. There is little exact information concerning visceral damage from straight convulsive shock, but it is certain that convulsions induced either by a drug or an electric current produce visceral petechial hemorrhages, with a consequent flare-up, for example, of latent pulmonary tuberculosis. Therefore, aside from the question of fracture, straight convulsive shock is no longer justified. The modification by preliminary curarization prevents the severe convulsions responsible for visceral damage.

Since the advent of electrically induced convulsions and resultant instantaneous unconsciousness without aura, the fear element is markedly lessened. The fear of post-treatment confusion still remains. In my opinion the best present method is combined curare-electric convulsive shock therapy. By this method traumatic complications are eliminated, initial fear is minimized and post-treatment discomfort is lessened. This method also offers obvious advantages over those of combined generalized anesthesia and metrazol convulsion. Focal necrosis of the brain resulting from anoxia has occurred many times from nitrous oxide anesthesia, even of short duration. One wonders whether another hazard might not be present with this combined technic.

It must be emphasized, however, that all the present methods are still empiric, and there are needed further refinements of technic and continued research to find the specific elements responsible for the cure of affective psychoses.

Dr. H. E. Himwich, Albany, N. Y.: I am interested in the possibility of improvement in the therapeutic results arising from Dr. Fabing's change in technic. When most of the shock therapies are analyzed, they are found to have in common an interference with the respiratory movements, so that the blood traversing the lungs is no longer fully saturated with oxygen. In fact, arterial blood begins to assume a venous color during the first part of the convulsion, a change which becomes more marked as the fit progresses. This does not apply to metrazol therapy alone; even when metrazol convulsions are softened with preliminary curarization, according to Dr. Bennett's procedure, the same phenomenon is observed. Apparently, interference with respiratory movements occurs then too. When metrazol convulsions are ameliorated by erythroidin, as suggested by Drs. Cameron and Rosen, of Albany, N. Y., again the same deficient oxygenation of arterial blood develops.

Electric shock therapy also interferes with respiratory movements, and in the reaction which has been termed "petit mal" there is a slight diminution in the oxygen saturation of the arterial blood. In the "grand mal" response, from which better therapeutic results are obtained, there may be a great reduction in the oxygen content of the blood. There therefore seems to be a connection between the reduction of the oxygen of the arterial blood and the therapeutic results. It has been suggested that on deprivation of the oxygen supply to the brain cerebral metabolism becomes depressed and that this depression may play a part in the beneficial therapeutic results. It is interesting that in reality Dr. Fabing employs two methods, which through reducing the oxygenation of the arterial blood act synergistically to depress brain metabolism. First, the volume of the oxygen entering the blood is reduced when the patient breathes the nitrous oxide-oxygen mixture; then the convulsive factor further intensifies this effect.

It would seem that Dr. Fabing's method might improve the therapeutic results because of a more profound depression of brain metabolism. I should like to

ask him whether it would not be advantageous to maintain breathing of the nitrous oxide mixture until convulsions begin, in order to sustain the anoxemic effect until the fit is initiated.

Dr. Howard Fabing, Cincinnati: I endorse Dr. Piker's note of caution. The simplification of the technic of administration of shock therapies, by one means or another, is prone to lead to their indiscriminate use, and this must be guarded against. Whether the anesthetized patient can experience fear is a speculative issue. I can only say that 2 of the patients who have been subjected to metrazol convulsive therapy under nitrous oxide anesthesia were physicians. I regard them as better observers of subjective phenomena than the average patient. They reported no sensation beyond that incident to the inhalation of the gas, and they were both entirely amnesic for the postconvulsive confusion period. I agree with Dr. Bennett that the series is a small one and that the percentage of traumatic complications might increase in a larger series. Further study alone will prove or disprove this point.

As for Dr. Himwich's remarks, I cannot say whether the results with this method are any better than those one usually gets. I am inclined to believe that they are. How much is due to a more cooperative, less frightened attitude on the part of the patient throughout the course of treatment I do not know. These patients do not object to treatment as the average unanesthetized patient does.

Whether it would be of value to continue the anesthesia until the fit starts, i. e., through the latent period, is problematic. At best there would be but two or three more inspirations during that period, so that the relative cerebral anoxia could not be altered profoundly. However, Fogel and Gray (Fogel, E. J., and Gray, L. P.: *Am. J. Psychiat.* **97**:676-685 [Nov.] 1940) have used nitrous oxide inhalation alone in the treatment of schizophrenia, and they report good results in cases of early disease. Therefore the adjuvant effect of the gas itself may be such that one should strive to prolong its inhalation.

EFFECT OF EMOTIONAL EXCITEMENT ON THE INSULIN CONTENT OF THE BLOOD

CONTRIBUTION TO PHYSIOLOGY OF THE PSYCHOSES

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AND

A. ALLEN

CHICAGO

It was shown recently [1] in experiments on cats and rats that the autonomic nervous system participates to a larger extent in the emotional process than would be anticipated from Cannon's classic studies. According to our investigations emotional excitement and hypothalamic stimulation are characterized by a discharge over both the vagoinsulin and the sympatheticoadrenal system, with predominance of the excitation of the latter. This result was shown particularly clearly in experiments on rats, in which it was found that normal rats reacted to emotional stimuli with hyperglycemia whereas adrenalectomized rats showed hypoglycemia in response to emotional excitement. That these two effects were due to a discharge over the sympatheticoadrenal and the vagoinsulin system respectively was proved by the observation that no changes in blood sugar resulted from emotional stimuli applied to vagotomized-adrenalectomized animals.

Subsequent studies of Gellhorn, Feldman and Allen [2] made it possible to assay insulin in minute quantities in the blood. The hypophysectomized-adrenodemedullated rat was used for the assay. Such a preparation reacts to the injection of 0.0002 unit of insulin per hundred grams rat weight with an appreciable fall in blood sugar. Since emotion

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A preliminary report of this work has previously been published (Gellhorn, E.; Allen, A., and Feldman, J.: Influence of Emotional Excitement on Insulin Content of Blood in Animals and Psychotic Patients, Proc. Soc. Exper. Biol. & Med. **46**:572, 1941).

1. Gellhorn, E.; Cortell, R., and Feldman, J.: The Autonomic Basis of Emotion, Science **92**:288, 1940.

2. Gellhorn, E.; Feldman, J., and Allen, A.: Assay of Insulin on Hypophysectomized, Adreno-Demedullated and Hypophysectomized-Adreno-Demedullated Rat, Endocrinology **29**:137, 1941; Am. J. Physiol. **133**:193, 1941.

involves both the sympatheticoadrenal and the vagoinsulin system, the chance of detecting insulin in the blood in increased amounts during emotional excitement in man would be greatest if subjects could be selected in whom the sympathetic nervous system responded less than in normal persons. The clinical and experimental literature cited in an earlier paper,[3] as well as the more recent experiments of Freeman and Rodnick,[4] suggests that this is true of schizophrenic patients. Moreover, Tauber and associates,[5] in an investigation of the bladder reflexes, found a stronger parasympathetic reaction in catatonic patients than in normal subjects. For this reason the influence of emotion on normal and on excited psychotic patients was investigated.

METHOD

Rats weighing approximately 100 to 130 Gm. were used for the assay of the insulin content of the blood. The hypophysis was removed through the pharyngeal approach, and after an interval of at least one week the adrenal glands were demedullated. Forty-eight hours later the animals were used, after they had been made to fast for six hours. The blood from the patients and from normal persons was obtained two hours after luncheon, coagulation being prevented by use of citrate. The blood of the patient and that of the rat prior to the injection of the patient's blood were analyzed for sugar; then, in less than five minutes after it had been drawn, 1 cc. of whole blood per hundred grams rat weight was injected intraperitoneally. One hour later a second sample of blood was obtained from the rat and the sugar content was assayed by means of the Somogyi modification of the Shaffer-Hartman method.

RESULTS

We first investigated whether the insulin content of normal persons and that of schizophrenic patients were different. Table 1 shows the results of the assay of the insulin of the blood of 10 normal persons. The blood sugar varied from 74 to 84 mg. per hundred cubic centimeters. The assay of the blood sugar made on the hypophysectomized-adrenodemedullated rat showed a slight but consistent fall after the injection of the blood. The blood of normal persons seems to contain approximately 0.0001 to 0.0002 unit of insulin per cubic centimeter.[2]

Table 2 shows results obtained on a series of nonexcited schizophrenic patients. The variation in sugar content of the patients' blood was

3. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System: A Basis for Rational Therapy of Schizophrenia, Arch. Neurol. & Psychiat. **40**:125 (July) 1938.

4. Freeman, H., and Rodnick, E. H.: Autonomic and Respiratory Responses of Schizophrenia and Normal Subjects to Changes of Intra-Pulmonary Atmosphere, Psychosom. Med. **2**:101, 1940.

5. Tauber, E. S.; Lewis, L. G., and Langworthy, O. R.: Vesical Activity in Schizophrenic States, Associated with Catalepsy, Arch. Neurol. & Psychiat. **39**:14 (Jan.) 1938.

approximately the same as that found in the blood of the controls (74 to 81 mg. per hundred cubic centimeters). The assay of insulin on the test rats revealed also a slight but consistent fall in blood sugar of the same magnitude as that found with the blood of the control. From these experiments it may be concluded that there are no significant

TABLE 1.—*Results of Assay of the Insulin Content of the Blood of Ten Control (Normal) Subjects*

Number	Subject's Blood Sugar, Mg. per 100 Cc.	Blood Sugar of Test Animal, Mg. per 100 Cc. *	
1	77.4	58.0	49.4
2	79.5	56.9	48.3
3	76.3	56.9	51.6
4	77.4	59.1	53.7
5	80.6	56.9	50.5
6	78.5	56.9	52.6
7	82.7	56.9	53.7
8	74.1	56.9	50.5
9	75.2	59.1	51.6
10	83.8	56.9	53.7

* In this table and in the succeeding tables, the blood sugar value of the hypophysectomized-adrenodemedullated rat before injection of blood is shown in the first column and that obtained one hour after the injection of 1 cc. of blood per hundred grams rat weight is shown in the second column.

TABLE 2.—*Results of Assay of the Insulin Content of the Blood of Nonexcited Schizophrenic Patients*

Number	Patient's Blood Sugar, Mg. per 100 Cc.	Blood Sugar of Test Animal, Mg. per 100 Cc.	
1	80.6	60.2	51.6
2	78.5	58.0	53.7
3	77.4	61.4	49.4
4	74.1	60.2	54.8
5	76.3	58.0	49.4
6	81.1	58.0	48.3
7	77.4	59.1	56.2
8	74.1	60.2	49.4
9	81.1	58.0	53.7
10	80.6	60.2	51.6

differences between the insulin content of the blood of normal persons and that of nonexcited schizophrenic patients when tested two hours after a meal.

The main series of experiments was performed on patients and normal persons during the state of excitement. No selection with regard to the form of the psychosis was made. The results obtained for excited psychotic patients may be best discussed on the basis of the blood sugar values found in these patients during emotional excitement.

In agreement with the investigations of Bowman and Kasanin,[6] Gildea and associates [7] and Whitehorn,[8] it was found that the majority of the excited patients showed normal values for blood sugar. In 21 patients the blood sugar varied from 70 to 85 mg. per hundred cubic centimeters, and only in 6 patients, to be discussed later, was the blood sugar value higher than 85 mg. per hundred cubic centimeters.

TABLE 3.—*Results of Assay of the Insulin Content of the Blood of Excited Psychotic Patients*

Number	Patient's Blood Sugar, Mg. per 100 Cc.	Blood Sugar of Test Animal, Mg. per 100 Cc.		Diagnosis
		Blood Sugar Not Elevated		
1	79.5	56.9	36.5	Manic-depressive psychosis
2	81.1	59.1	33.3	Psychosis due to other metabolic disturbances
3	81.1	58.0	35.4	Psychosis due to other metabolic disturbances
4	80.6	59.1	37.6	Schizophrenia
5	83.8	60.2	29.0	Schizophrenia
6	79.5	58.0	33.3	Dementia paralytica
7	78.5	60.2	32.2	Paranoid psychosis
8	81.1	59.1	36.5	Schizophrenia
9	79.5	62.3	38.7	Dementia praecox
10	73.1	61.2	35.4	Dementia praecox
11	84.9	59.1	34.4	Dementia paralytica
12	69.8	56.9	32.2	Schizophrenia
13	74.1	56.9	32.2	Schizophrenia
14	82.7	59.1	38.7	Catatonic schizophrenia
15	77.4	59.1	35.4	Schizophrenia
16	74.1	60.2	39.7	Schizophrenia
17	84.9	60.2	34.4	Acute schizophrenia
18	75.2	58.0	39.7	Schizophrenia
19	77.4	60.2	36.5	Schizophrenia
20	80.6	56.9	34.4	Schizophrenia
21	82.7	60.2	34.4	Schizophrenia
		Blood Sugar Elevated		
1	107.5	58.0	59.1	Acute schizophrenia
2	109.2	59.1	45.1	Schizophrenia
3	102.1	59.1	49.4	Schizophrenia
4	94.6	60.2	39.7	Dementia praecox
5	132.5	61.2	56.9	Manic-depressive psychosis
6	109.2	60.2	50.5	Schizophrenia

When assays of the insulin content of the blood of excited patients were made on hypophysectomized-adrenodemedullated rats, a consistent reaction appeared which differed fundamentally from that observed in the nonexcited control and schizophrenic groups. In all 21 observa-

6. Bowman, K. M., and Kasanin, J.: The Sugar Content of the Blood in Emotional States, Arch. Neurol. & Psychiat. **21**:342 (Feb.) 1929.

7. Gildea, E. F.; Mailhouse, V. L., and Morris, D. P.: The Relationship Between Various Emotional Disturbances and the Sugar Content of the Blood, Am. J. Psychiat. **92**:115, 1935.

8. Whitehorn, J. C.: The Blood Sugar in Relation to Emotional Reactions, Am. J. Psychiat. **13**:987, 1934.

tions [9] it was found that the blood obtained from the excited patients produced a hypoglycemic reaction in the test animal and caused typical hypoglycemic symptoms. The animal lay on its side and did not show any righting reflexes; occasionally hypoglycemic convulsions were observed. The analysis of the blood sugar of the test animal showed very low values, varying between 29 and 40 mg. per hundred cubic centimeters. In no case were values observed similar to those obtained with the blood of nonexcited normal persons or psychotic patients. In view of the fact that the hypoglycemic reaction of the hypophysectomized-adrenodemedullated animal is specific for insulin (Gellhorn, Feldman and Allen [10]), the occurrence of severe hypoglycemia indicates that the blood contains more insulin than normal. Moreover, the absence of any hyperglycemic effect on their own blood suggests that in this group of patients emotional excitement is accompanied by no

TABLE 4.—*Results of Assay of the Insulin Content of the Blood of Excited Normal Persons*

Number	Subject's Blood Sugar, Mg. per 100 Cc.	Blood Sugar of Test Animal, Mg. per 100 Cc.	
1	96.8	60.2	64.5
2	94.6	58.0	58.0
3	92.5	59.1	59.1
4	98.9	56.9	64.5
5	99.9	58.0	61.2
6	102.1	58.0	59.1 (Labor, 7 hr.)

appreciable increase in the amounts of epinephrine in the blood, but by a greatly increased secretion of insulin.

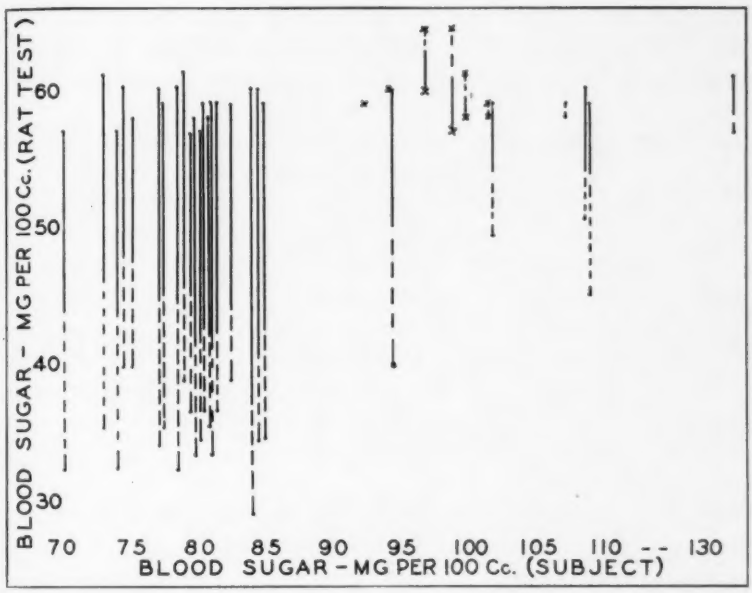
Although the majority of psychotic patients seem to show no hyperglycemic effects from emotional excitement, it is to be expected that some would show reactions somewhat intermediate between those of normal persons and those of the psychotic group which was just described. In fact, Whitehorn [8] and others have observed occasional

9. In 1 instance the injection of blood of the excited patient produced no change in blood sugar in the hypophysectomized-adrenodemedullated rat. The initial blood sugar value before injection was 60.2 mg. per hundred cubic centimeters and the value after injection was 59.1 mg. Such a response, in which there was absent even the slight hypoglycemic effect produced on the test animal by blood of a normal subject, is characteristic of incomplete hypophysectomy. In a number of experiments similar values were found when animals with incomplete hypophysectomy were used. In this particular case no remnants of the hypophysis were found macroscopically, but it seems safe to conclude that microscopic remnants must have remained in the test animal.

10. Gellhorn, E.; Feldman, J., and Allen, A.: The Insulin Concentration in the Blood of Normal and Pancreatectomized Dogs, Endocrinology **29**:849, 1941.

cases of hyperglycemia among excited psychotic patients. Our own observations showed increased values for blood sugar in 6 patients. When the blood obtained from these patients was tested on the hypophysectomized-adrenodemedullated rats, it was found that all but 1 animal showed hypoglycemic reactions of various degrees. The experiments indicate that sufficient insulin has been liberated in these patients during emotional excitement to offset the effects of the simultaneously increased epinephrine content of the blood.

The significance of these results becomes clear when they are compared with observations on the effect of emotional excitement on the



The effect of emotional excitement on the insulin content of the blood in normal subjects and in psychotic patients.

The blood sugar values for the subjects are indicated on the abscissa. The effect of the injection of 1 cc. of blood per hundred grams hypophysectomized-adrenodemedullated rat are indicated on the ordinate.

The initial and the final blood sugar of the test animal are connected by a line which near the initial value is continuous and near the final value is interrupted. The tests made with the blood of excited psychotic patients are indicated by lines with dots; those made with the blood of excited normal controls, by lines with crosses.

blood sugar and insulin content of the blood of normal subjects. Excitable students who were subjected to a three hour examination in physiology were used as experimental subjects. The blood sugar ranged from 93 to 102 mg. per hundred cubic centimeters, indicating mild hyper-

glycemia, which was definitely less pronounced than that found in the hyperglycemic group of excited psychotic patients. The tests on hypophysectomized-adrenodemedullated rats gave results which were fundamentally different from those obtained for excited psychotic patients. The blood sugar of the test animals was either unchanged or very slightly increased as a result of the injection of the blood from these excited normal subjects. These experiments indicate that when the blood sugar is raised appreciably in normal persons the amount of epinephrine present in the blood is adequate to offset the effects of its insulin content on the test animal.

It was described in the experiments reported thus far that fundamental differences exist between the insulin content of the blood of normal and that of psychotic subjects under conditions of excitement, although such differences are absent when nonexcited patients are

TABLE 5.—*Reversibility of the Effect of Excitement on the Insulin Content of the Blood of Psychotic Patients*

Patient	Patient's Blood Sugar, Mg. per 100 Cc.	Blood Sugar of Test Animal, Mg. per 100 Cc.		Diagnosis
P, excited	79.5	56.9	36.5	Manic-depressive psychosis
P, not excited	74.1	60.2	54.8	Manic-depressive psychosis
D, excited	81.1	59.1	33.3	Psychosis due to other metabolic disturbances
D, not excited	76.3	58.0	49.4	
M, excited	83.8	60.2	29.0	Schizophrenia
M, not excited	74.1	60.2	49.4	Schizophrenia
B, excited	102.1	59.1	49.4	Schizophrenia
B, not excited	81.1	58.0	53.7	Schizophrenia

tested. This conclusion is further supported by investigations on 4 patients who were once tested during a state of excitement and then after the excitement had subsided. The results reproduced in table 5 show clearly that the insulin content of the blood of these patients is similar to that found in other, nonexcited patients or in normal persons.

COMMENT

The results of investigations reported in this paper show clearly that the insulin content of the blood of normal and that of psychotic subjects are the same. Apparently, psychotic and normal persons do not differ with regard to the secretion of insulin in periods of rest but differ only with respect to the reactivity of the autonomic centers controlling the secretion of insulin via the vagus nerve and the recreation of epinephrine via the sympathetic system. Studies by Gellhorn, Cortell and Feldman [11] showed that hypothalamic stimulation leading to the syndrome

11. Gellhorn, E.; Cortell, R., and Feldman, J.: The Effect of Emotion, Sham Rage and Hypothalamic Stimulation on the Vago-Insulin System, Am. J. Physiol. **133**:532, 1941.

of sham rage, as well as emotional excitement, produced in unanesthetized animals a discharge over both the vagoinsulin and the sympathetico-adrenal system, the effect on the latter predominating. Such a predominance is observed in normal persons under conditions of emotional excitement and results in hyperglycemia. Psychotic persons, however, show a fundamentally different reaction, inasmuch as they fail to raise their own blood sugar under conditions leading apparently to marked degrees of general excitation. Since sham rage and emotional excitement lead to similar alterations in the autonomic balance (Gellhorn, Cortell and Feldman [11]), the question whether psychotic persons experience emotional excitement or display it is not of importance. As a matter of fact, the cortical component of the emotional process does not contribute to the degree of autonomic discharge except by inhibiting it. Therefore the fundamental difference in the blood sugar reactions of normal and of psychotic persons under conditions of excitement points to a lesser responsiveness of the centers of the sympatheticoadrenal system in the latter.

It is to be expected that between normal persons and psychotic patients, characterized by a weakness in the reactivity of the sympathetic centers, there would be an intermediate group in which the sympatheticoadrenal system would react in an approximately normal fashion in spite of the presence of a psychosis. This group is represented by 6 out of 27 cases in which "emotional excitement" led to an increased level of the blood sugar.

The assay of insulin in the blood of normal persons and of psychotic patients gives further insight into the conditions of the autonomic centers in emotional excitement. The fact that hypophysectomized-adrenodemedullated rats react invariably with marked hypoglycemia to the injection of blood obtained from excited psychotic patients in whom the blood sugar value remained unaltered during the period of excitement indicates clearly that insulin is secreted in increased amounts in these patients under conditions of emotional excitement. Accordingly, it must be assumed that these patients react to the emotional stimulus with a discharge which involves exclusively or predominantly the vagoinsulin system. Such an interpretation is based on the fact that the hypophysectomized-adrenodemedullated rat does not react to those quantities of epinephrine which are normally present in the blood.[2] When the blood sugar is unchanged in the patient's blood the result on the test animal is solely determined by the insulin concentration present in the blood.

On the other hand, blood obtained from normal persons during emotional excitement failed to elicit even the slight hypoglycemic reaction on the test animals which was observed when blood from unexcited normal persons was injected. This is due to the fact that the increased epinephrine concentration in the blood is sufficient to mask

completely the effect of the normal insulin content of the blood on the blood sugar of the test animal. Although an attempt will be made in later experiments to separate epinephrine and insulin in the blood of normal subjects and of patients under conditions of excitement, the experiments show clearly that this condition elicits predominantly an increase in epinephrine content unaccompanied by significant alterations in the insulin concentration in normal persons whereas the majority of psychotic patients showed only increased amounts of insulin in the blood during excitement, without any rise in the epinephrine concentration.

It was mentioned before that 6 psychotic patients showed a rise in blood sugar during a state of emotional excitement, a fact indicating that the sympatheticoadrenal system was reacting adequately. Since the blood sugar values were considerably higher for these patients than for our excited normal controls, it may be said that more epinephrine was secreted by these patients than by the control subjects subjected to a relatively slight emotional stimulus. In spite of this fact it is found that the blood of the former when injected into the hypophysectomized-adrenodemedullated rats elicited a hypoglycemic reaction in the test animals whereas the injection of blood obtained from the excited control subjects caused either no change in or a rise in blood sugar in the test animals. This proves conclusively that the balance of the autonomic centers is fundamentally different in normal and in psychotic persons. This statement applies also to those patients who react to excitement with hyperglycemia.

Although according to the clinical diagnosis the condition of the majority of patients studied belongs to the schizophrenic group, the observations seem to suggest that the disturbance in the reactivity of the autonomic centers is by no means restricted to this form of mental illness. Only further investigations can clarify the significance of these findings for various forms of mental disease.

It is noteworthy that the amount of insulin observed in the blood of nonexcited schizophrenic patients is similar to that observed in the blood of normal persons. Apparently the humoral factors regulating by peripheral mechanisms the secretion of insulin are not affected in these patients, but the reactivity of the autonomic centers controlling the output of these hormones (insulin and epinephrine) is altered.

Several authors (Hoskins,[12] Pfister,[13] Wespi[14] and others) suggested weakness of the sympatheticoadrenal system in schizophrenia on

12. Hoskins, R. G.: Oxygen Metabolism in Schizophrenia, Arch. Neurol. & Psychiat. **38**:1261 (Dec.) 1937.

13. Pfister, H. O.: Die neuro-vegetativen Störungen der Schizophrenien und ihre Beziehungen zur Insulin-, Cardiazol- und Schlafkurbehandlung, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:77, 1937.

14. Wespi, H.: Vorläufige Mitteilung über Beobachtungsresultate von vegetativen Funktionen bei der Insulinshockbehandlung Schizophrener, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:83, 1937.

the basis of the response of the patient to various environmental stimuli. The results of these investigations showed only quantitative differences between normal and schizophrenic patients and a considerable overlap of the two groups. By taking the vagoinsulin system into account and by using the hypophysectomized-adrenodemedullated rat as a test animal a fundamental difference in the reactivity of autonomic centers between normal and psychotic subjects was discovered. These observations are of importance for the understanding of the physiologic mechanism of the shock therapy. In 1938 Gellhorn showed that the various forms of shock therapy have one factor in common, the prolonged excitation of the centers of the sympathetic system. This holds true also for electric shock (Kessler and Gellhorn [15]). This analysis and the proof of the imbalance of the autonomic centers in psychotic persons presented in the investigations reported in this paper form the rational basis of the shock therapy of psychoses. The most important problem is to determine how disturbances in the autonomic centers affect the cortex.

It is of interest to discuss the possible factors involved in the reversal of the responsiveness of the autonomic centers in psychotic patients as compared with normal persons. Investigations by Gellhorn and Feldman [16] showed that the thyroid hormone has a specific effect on the excitability of the centers of the sympatheticoadrenal system. Thyroidectomy leads to a decrease in the responsiveness of the center of the sympatheticoadrenal system without altering the reactivity of the vagoinsulin system. Conversely, it was found that the injection of thyroxin greatly increased the reactivity of the sympathetic centers as tested by the blood sugar response to metrazol and electric shock while it did not alter the vagoinsulin system. These observations are of interest in view of the fact that according to several authors (Hoskins and Sleeper,[18] Rheingold [19] and others) a thyroid deficiency not infrequently accompanies schizophrenia.

15. Kessler, M., and Gellhorn, E.: Effect of Electrically Induced Convulsions on Vago-Insulin and Sympathetico-Adrenal Systems, Proc. Soc. Exper. Biol. & Med. **46**:64, 1941.

16. Gellhorn, E., and Feldman, J.: The Influence of the Thyroid on the Vago-Insulin and Sympathetico-Adrenal Systems, Endocrinology **29**:467 (Sept.) 1941.

17. Gellhorn, E., and Feldman, J.: The Effect of Magnesium Deficiency on the Excitability of the Vago-Insulin and Sympathetico-Adrenal Systems, Am. J. Physiol. **134**:603, 1942.

18. Hoskins, R. G., and Sleeper, F. H.: The Thyroid Factor in Dementia Praecox, Am. J. Psychiat. **10**:411, 1930.

19. Rheingold, J. C.: Autonomic Integration in Schizophrenia, Autonomic Status Determined Statistically, the Thyroid Factor and a Possible Thyroid-Hypothalamus Mechanism, Psychosom. Med. **1**:397, 1939.

From a therapeutic standpoint it seems of interest to point out that the thyroid hormone is by no means the only factor determining the excitability of the autonomic centers. It was recently found that magnesium or calcium deficiency (Gellhorn and Feldman [17]) greatly increases the excitability of the centers of the sympatheticoadrenal system and markedly diminishes the reactivity of the centers of the vagoinsulin system. Whereas thyroidectomy diminishes the predominance of the sympatheticoadrenal system without affecting the vagoinsulin system, deficiency in magnesium or calcium seems to increase greatly the reactivity of the sympatheticoadrenal centers. Such studies make it not improbable that dietary measures may alter the responsiveness of autonomic centers in the human being. If it is true that the reactivity of these centers plays an important part in the development of the psychosis, these observations suggest new therapeutic avenues of approach for mental disease.

SUMMARY

The insulin content of human blood is assayed with the hypophysectomized-adrenodemedullated rat. It is shown that normal and psychotic persons have the same amount of insulin in the blood in the absence of emotional excitement. Under conditions of emotional excitement, however, the insulin content of the blood is greatly increased in psychotic patients. If under these conditions their own blood sugar is unchanged (and this was the case in 21 of 27 cases), an increased insulin concentration in the blood leads to a marked fall in blood sugar of the test animal, accompanied by coma. If the blood sugar level is raised (6 cases out of 27), it may cause this hypoglycemic syndrome in the test animal in spite of the increased epinephrine concentration of the blood. Normal persons, however, under conditions of excitement showed a slight rise in the blood sugar, and their blood produced no hypoglycemic reaction whatever in test animals. The experiments are interpreted to mean that the balance of the autonomic centers in psychotic patients under emotional stress is shifted toward the vagoinsulin side whereas in normal persons the sympatheticoadrenal system greatly predominates.

MOMENTARY DEATH AND CHOREOATHETOSIS FOLLOWING NITROUS OXIDE ANESTHESIA WITH RECOVERY

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Many reports [1] have recently appeared describing damage to the brain following the use of nitrous oxide anesthesia, the pathologic changes being found predominantly in the cerebral cortex and the basal ganglia. Most of the patients die during the anesthesia or a short time thereafter. Sudden death, coma, convulsions, decerebrate phenomena, delirium, paralysis, hyperthermia, visual defects, aphasias and amnesia and mental and psychic changes have been reported in various combinations, with partial or complete recovery. The appearance of a clearcut clinical picture of extrapyramidal disease characterized mainly by choreoathetosis is rare.

In 1887 Savage [2] cited a case of delirium in which "irregular movements of all kinds were being made." The patient finally became demented and was placed in an institution, where she remained "silly and fat." In only 1 of Caine's [3] 4 cases, reported in 1923, did choreo-

1. (*a*) Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129-245 (May) 1936. (*b*) Löwenberg, K.; Waggoner, R., and Zbinden, T.: Destruction of Cerebral Cortex Following Nitrous Oxide-Oxygen Anesthesia, Ann. Surg. **104**:801-810 (Nov.) 1936. (*c*) Löwenberg, K., and Zbinden, T.: Destruction of Cerebral Cortex Following Nitrous Oxide-Oxygen Anesthesia, Anesth. & Analg. **17**:101-108 (March-April) 1938. (*d*) Abbott, C. N., and Courville, C. B.: Degeneration of Globus Pallidus After Anesthesia: Case with Survival Period of Forty-Two Days, Bull. Los Angeles Neurol. Soc. **3**:46-50 (March) 1938. (*e*) Courville, C. B.: Pathogenesis of Necrosis of Cerebral Gray Matter Following Anesthesia, Ann. Surg. **107**:371-379 (March) 1938. (*f*) O'Brien, J. D., and Steegmann, A. T.: Severe Degeneration of Brain Following Nitrous Oxide-Oxygen Anesthesia, ibid. **107**:486-491 (April) 1938.

2. Savage, G. H.: Insanity Following the Use of Anesthetics in Operations, Brit. M. J. **2**:1199 (Dec. 3) 1887.

3. Caine, A. M.: Some Unusual Complications of Nitrous Oxide-Oxygen Anesthesia, Am. J. Surg. (supp.) **37**:34-36 (April) 1923.

athetoid movements develop as part of a residual picture, accompanied by visual impairment and difficulty in speech. In 1931 Yaskin [4] reported a case in which choreiform movements played a minor part in a neurologic picture which included coma, dysarthria, dysphagia, limited extraocular movements and impairment of vision. In the fifth of Courville's [1a] 13 cases reported in 1936 the patient lived four days and seven hours, with coma, generalized muscular twitchings, decerebrate rigidity, and, on occasion, choreiform movements. In his ninth case the patient lived twenty-six days and presented coma, convulsions and blindness, and later confusion and frequent and violent aimless, uncontrollable movements of the extremities. Only in his eleventh case did the patient survive and a clearcut lenticular syndrome develop; this case was reported in greater detail in another communication.[5] In 1938 Stewart [6] described a case in which the patient exhibited facial grimaces and aimless waving and choreiform movements of the arms for forty-eight hours, then lapsed into coma and died twelve days after the administration of nitrous oxide.

Thus we have found reference to only 6 cases in which choreoathetoid movements are mentioned, and here solely in relation to the protean symptomatology subsequent to nitrous oxide anesthesia. Most of these reports are brief. We are reporting a case in which choreoathetosis appeared as the major symptom. Besides its unusual neurologic aspects, we believe this case will serve to call attention to the late clinical effects of nitrous oxide asphyxia, which are rarely seen except by the specialist.

REPORT OF A CASE

J. C., a 33 year old Negro, married, was admitted to the urologic service of a local hospital on Nov. 5, 1940, with the complaint of increasing difficulty in urination in the past year and retention of urine for the past two days. Except for an attack of gonorrhea about five years previous to admission, his past history was essentially noncontributory. He had been born and raised and attended school in Curacao, Netherland West Indies, reaching the seventh grade. For the past fifteen years he had worked on ships as waiter, cook and cabin boy. His shipmates' impression of the patient indicated that he had always been quiet, kept to himself, was not very friendly, at times seemed depressed, got upset over trifles and had outbursts of temper.

Physical examination on admission revealed that the patient was well nourished and well developed. There was a stricture of the urethra which would admit only a filiform catheter, and the urinary flow was ragged and weak. The other systems were normal. The chemical constituents of the blood were normal; the Wasser-

4. Yaskin, J. C.: Nonsuppurative Nonepidemic Encephalitis Following Labor and in the Puerperium, Arch. Neurol. & Psychiat. **26**:371-391 (Aug.) 1931.

5. Courville, C. B.: Lenticular Syndrome Following Nitrous Oxide Narcosis, Bull. Los Angeles Neurol. Soc. **1**:30 (March) 1936.

6. Stewart, J. D.: Cerebral Asphyxia During Nitrous Oxide and Oxygen Anesthesia, New England J. Med. **218**:754-757 (May 5) 1938.

mann reaction was negative, and the urine was essentially normal. On November 7 an external urethrotomy was performed with the patient under anesthesia induced by 150 mg. of procaine hydrochloride injected intraspinally. Several strictures were found in the anterior bulbous portion of the urethra and one or more false passages in the anterior wall of the urethra. After operation the wound bled daily at intervals, and during these hemorrhages the patient became apprehensive and depressed. His hemoglobin concentration fell from 90 per cent on November 7 to 35 per cent on November 16. On November 16 he was taken to the cystoscopy room, and, while under spinal anesthesia induced by 50 mg. of procaine hydrochloride, the wound was repacked. Transfusion of 500 cc. of blood was given on November 20. On November 22 the wound suddenly bled profusely and he was taken to the operating room.

He was given a preanesthetic injection of ¼ grain (0.016 Gm.) of morphine sulfate and 1/150 grain (0.4 mg.) of atropine. Anesthesia (induced by 85 to 89 per cent nitrous oxide, 11 to 15 per cent oxygen and ½ ounce [14.7 cc.] of ether) was begun at 2:07 p. m. Infusion of physiologic solution of sodium chloride was started, and the operation began at 2:22 p. m. At 2:50 p. m. a transfusion of 500 cc. of whole citrated blood was given. No cyanosis was noted, but the respirations were spasmodic throughout the operation. At 3 p. m. the patient suddenly ceased breathing, his heart sounds could not be heard and the pulse and blood pressure were unobtainable. One cubic centimeter of epinephrine hydrochloride was given intracardially, and caffeine and coramine (25 per cent solution of pyridine betacarbonic acid diethylamide) were administered intravenously. After an estimated period of about two minutes he began to breathe somewhat rapidly and his blood pressure gyrated wildly. At 3:08 p. m. his blood pressure was 215 systolic and 110 diastolic, his pulse rate 160 and his respiratory rate 25. The operation and anesthesia ended at 3:15 p. m. The postoperative condition was poor; the pulse was variable in strength, and the blood pressure rose and fell. By 10 p. m. his blood pressure was 120 systolic and 68 diastolic, his pulse rate 88 and his respiratory rate 26. At midnight his temperature suddenly rose to 106 F., his pulse rate to 146, his respiratory rate to 34 and his blood pressure was 105 systolic and 56 diastolic. He was restless, perspiring and apprehensive. Physical examination revealed moderate pneumothorax on the left, with shifting of the trachea and mediastinum to the right. This was confirmed roentgenographically.

The following morning, November 23, it was noted that he was confused and incoherent, moved his arms restlessly about in bed and would not keep an ice cap on. He giggled at intervals and at other times displayed what was called "an amused expression on his face." In the afternoon he was noisy and uncooperative and threw himself around, so that sideboards were placed on his bed. Four people were required to give him medication. All evening his marked motor restlessness continued, he refused medication and thrashed about. He defecated in bed. He continued this behavior, at times was observed masturbating in bed or pulling at his dressings, and on November 29 it became necessary to apply a camisole. The following day he was moved to a private room because of the disturbance he was causing in the ward. He struck out at nurses and attendants and required constant restraints and much sedation. On December 2 it was noted that his speech was thick and slurring. The motor overactivity was continuous. At intervals there were short lucid periods in which his orientation appeared intact. His temperature fell to 101 F. by November 25 and remained between this level and normal.

His abnormal mental state persisted, and on December 6 he was transfered to the psychiatric division of Kings County Hospital. He had been given 1 ounce (29.5 cc.) of paraldehyde rectally to facilitate transfer and on arrival was in coma.

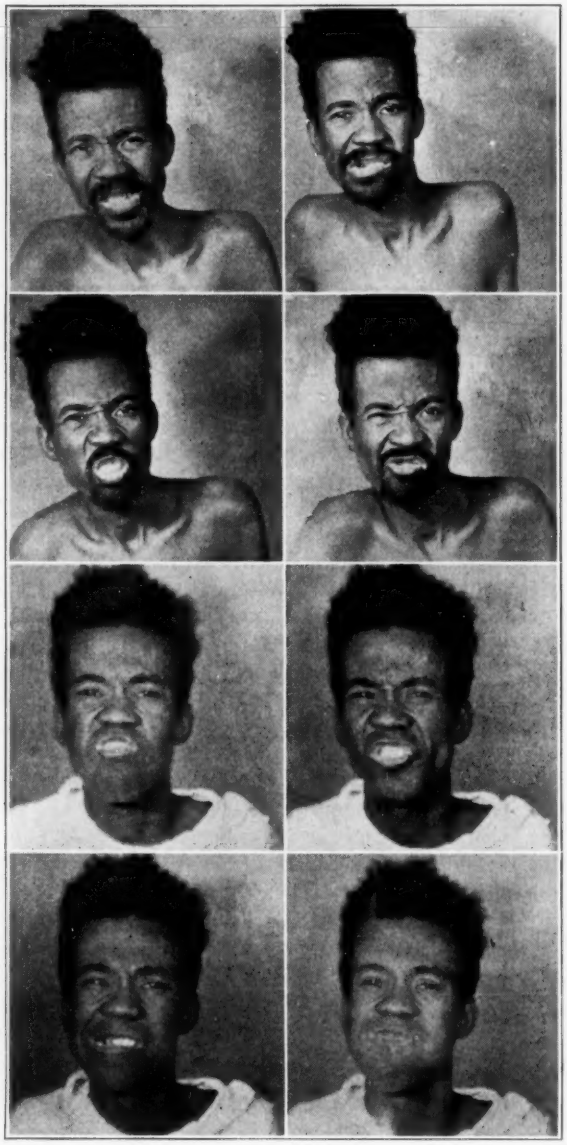

Fig. 1.—Typical involuntary movements of the face.

Examination at this time revealed the left pneumothorax with mediastinal shift, multiple pressure sores over bony prominences and a small granulating perineal urethrotomy wound.

On the following morning, December 7, he presented an entirely different picture. At this time there was marked motor restlessness consisting of grotesque, twisting, slow, nonrhythmic, irregular, patternless movements involving all the fingers, both hands, forearms and arms, the shoulders, the mouth, the jaw, the tongue and the facial muscles. The lower extremities and body were quiet. He was awake and appeared in contact with his environment. The pupils were equal and reacted to light. His speech was markedly nasal and dysarthric and was distorted by the rapid succession of involuntary movements of the mouth and tongue. He attempted to carry out simple commands, but these, too, were interfered with. He told his name, but his other responses could not be understood. During the examination it was noticed that he suddenly underwent periods of spontaneous extension spasms lasting about five to ten seconds. These involved the neck, spine and extremities and relaxed as suddenly as they developed. During these periods it was impossible to flex the extremities passively. There was a Babinski response on the left. The remaining deep and superficial reflexes were equal and active. The fundi were normal. Sensation was apparently intact. The surgical and medical status were as noted previously. A spinal tap revealed crystal clear fluid under normal pressure. The Wassermann reaction was negative. The colloidal gold curve was 1122221000, and there were 3 lymphocytes per cubic millimeter. The sugar content of the fluid was 72 mg. per hundred cubic centimeters and the total protein 36 mg. The blood count revealed 3,760,000 red cells; 73 per cent hemoglobin (Sahli), or 10 Gm. per hundred cubic centimeters, and 9,250 white cells, with 69 per cent polymorphonuclear leukocytes, 28 per cent lymphocytes and 3 per cent eosinophils.

The patient began to show signs of dehydration; the choreoathetoid movements prevented swallowing of fluids, and he had a fever, with a temperature between 101 and 103 F., for the next four days. Fluids were forced; infusions were given, and $\frac{1}{100}$ grain (0.6 mg.) of scopolamine hydrobromide was administered at regular intervals. The temperature fell to normal and remained there. The neurologic status remained unchanged for the next few days, the involuntary movements described interfering with a complete examination. The patient seemed willing to cooperate, asked for fluids and knew he was in a hospital, but his speech was hardly intelligible. By December 10 the choreoathetotic movements had diminished sufficiently to permit further contact. The patient was oriented approximately for time, place and person, cooperated well during the examination, understood laterality and pointed correctly to the various members of his body. The movements had all diminished but were most marked in the facial muscles and the tongue, interfering with speech. Except for a left Babinski reflex and confirmatory signs and absence of the left cremasteric reflex, all deep and superficial reflexes were intact. He still showed intervals of involuntary spasm of the extremities, lasting a few seconds. Sensation was intact in all modalities. The finger to nose and heel to knee test were performed without ataxia. The signs of pneumothorax remained; the patient voided urine from the perineal wound. To avoid the possible complications of hypostatic pneumonia, the patient was allowed up in a chair. During the remainder of his stay at the hospital he continued to improve and became ambulant. The pneumothorax was completely absorbed on December 24, both clinically and roentgenographically. Urethra sounds were passed biweekly, and on discharge the urethrotomy wound was practically healed and the patient was

voiding normally. The movements of the upper extremities gradually diminished, but the patient continued to demonstrate slow wandering movements of the fingers, which acted as an extended unit from the metacarpophalangeal joints. Speech cleared with the diminution of the involuntary movements, but a few choreoathetoid movements of the tongue and mimetic musculature persisted, which were much accentuated on his attempting to perform various tasks. By December 24 there had developed and remained moderate cogwheel rigidities of both upper extremities, and to a lesser extent of both lower extremities. At times sustained or transient ankle clonus was demonstrable. Visual fields, determined on December 28, were normal.

The patient was discharged on January 7, forty-six days after receiving nitrous oxide. On discharge he was in good spirits, quiet and cooperative. He complained of inability to sleep well and said "I feel weak, but I'm getting better every day." He was well oriented, conversed readily in English, French, Spanish and Dutch with various persons in the wards and responded to humor with the proper facial lability. When asked about his involuntary movements, he said, "I don't know; since I've been here I've been doing this. It comes on by itself, and I can't stop it." He spoke clearly but slowly and was easily understood. At times, however, the movements increased sufficiently to distort the speech for a few phrases. The pupils were equal and regular and reacted to light, both directly and consensually, and in accommodation. Extraocular movements were normal. There was no nystagmus. The fundi showed normal disks and vessels. Blinking was normal. The visual fields were intact. There was slight flattening of the left nasolabial fold, with a slight weakness of the left side of the face of central type. The tongue protruded in the midline. The pterygoid and sternocleidomastoid muscles were normal. Both shoulders could be elevated well. Air conduction was greater than bone conduction bilaterally, and the sound of the tuning fork was lateralized normally. Facial sensation and corneal and gag reflexes were intact.

Gait was somewhat slow and rigid, with mild diminution of the arm swings. At rest he exhibited various involuntary sucking, clicking and puffing movements of his tongue and mouth. He would suddenly close one or both eyes tightly, and one or the other side of his mouth would be pulled laterally, all in an irregular, patternless, nonrhythmic, contorted fashion. When he attempted voluntary movements or concentrated on a task, these involuntary movements would all be accentuated in frequency and amplitude. With the arms extended, the fingers, acting as an extended unit from the metacarpophalangeal joints, wandered irregularly up and down. Intricate and finer movements of the hands were performed without ataxia, but in a slow and clumsy way, the fingers being held stiff. There were no tremors or other involuntary movements. Moderate cogwheel rigidity was demonstrable in both shoulders, elbows and wrists, and to a lesser extent in both hips and knees. Motor power was good in all muscles. The deep reflexes were all equal, except for the triceps and the knee jerk on the left, which were hyperactive and slightly greater than those on the right. There was no clonus. The Babinski response and all the confirmatory signs were present on the left; the left cremasteric reflex was absent; the Hoffmann reflex was not elicited, and abdominal reflexes were equal and active on the two sides. All sensation was intact. The finger to nose and heel to knee tests were performed well. The Romberg test gave negative results; check and rebound phenomena were normal, and there was no adiadokokinesis.

On December 24, 25 and 26 the patient was examined by Mr. Solomon Machover, senior psychologist, with a comprehensive battery of objective, standardized psychologic tests. The Rorschach protocol was marked by predominence of global perceptions, with corresponding inadequacy of fine form discriminations. This disturbance in the perception of form, the anxious, depressed tone of the responses, the evidence of reduced affective inhibition and the indications of morbid preoccupation with sadistic and masochistic ideas of mutilation all pointed to a cerebral lesion. The patient's response to psychometric tests was variable, depending on the nature of the task to be performed. Although his scores on tests of comprehension and general information indicated essentially average native intellectual capacity, defects in rote memory and in creative organization of form perception, evidently a result of cerebral changes, were so severe as to reduce

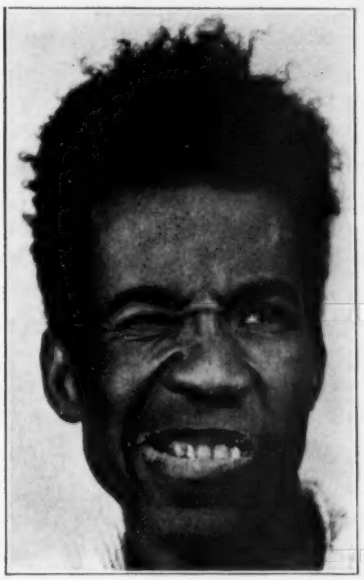

Fig. 2.—Involuntary movements of the face.

the final ratings to the defective level. The results of these psychologic tests confirmed the clinical impression and illustrated the importance of an integrated psychobiologic approach to cases of this character.

COMMENT

Nitrous oxide is a relatively weak anesthetic. Leake and Hertzman,[7] working on dogs, showed that in order to maintain surgical anesthesia with this gas some degree of anoxemia was required. Many other

7. Leake, C. D., and Hertzman, A. B.: Blood Reaction in Ethylene and Nitrous Oxide Anesthesia, J. A. M. A. **82**:1162-1165 (April 12) 1924.

investigators [8] have since verified this observation, and recently Murphy [9] warned that it is the cerebral anoxemia, and not primarily the nitrous oxide, which causes relaxation of muscle. According to Courville,[10c] it is this anoxemia which is responsible for the cerebral damage. This author, and others, have noted the frequency of temporary respiratory failure, with or without cardiac failure, during anesthesia. Downs,[10] experimenting with dogs, reported that such respiratory failure is due to pressure on the carotid sinus, which has been sensitized in some way by the administration of nitrous oxide. Löwenberg and his co-workers,[11] however, expressed the belief that nitrous oxide acts in a specific toxic manner on the central nervous system. It is well known that inhalation of carbon monoxide in illuminating gas or from automobile exhausts may be followed by permanent and varied neurologic residua.[12] Yet Mackay,[12b] in reviewing the literature on this subject, showed that there was by no means complete agreement as to whether the damage was done by lack of oxygen, noxious foreign substances in the gas or exhaust or the carbon monoxide itself. Gildea and Cobb [13] described the pathologic changes in the nervous system of cats following experimentally induced anoxemia. Recent workers,[14] using nitrogen inhalation to produce anoxemia for the treatment of mental diseases, have indicated that up to a certain point reversible motor phenomena are produced, but that further anoxemia may lead to less reversible effects. It is evident that the final word on this subject has not yet been written. Certainly, in those cases in which respiratory failure and death from nitrous oxide anesthesia occur very shortly after the onset of induction the role of anoxemia cannot be a major one. However, when anesthesia

8. Greene, C. W., and Currey, H. M.: The Respiratory Gas Percentages During Anesthesia in Dogs, Arch. Int. Med. **35**:371-379 (March) 1925. Macklin, A. H.: The Asphyxial Element in Gas-Oxygen Anesthesia, Lancet **2**:879-901 (Oct. 24) 1931. Brown, W. E.; Lucas, G. H. W., and Henderson, V. E.: The Anesthetic Value of Nitrous Oxide Under Pressure, J. Pharmacol. & Exper. Therap. **31**:269-289 (Aug.) 1927.

9. Murphy, F. J.: Anesthesia and Anoxemia in Relation to the Use of Nitrous Oxide, Surg., Gynec. & Obst. **70**:741-743 (April) 1940.

10. Downs, T. M.: Carotid Sinus as an Etiological Factor in Sudden Anesthetic Death, Ann. Surg. **99**:974-984 (June) 1934.

11. Löwenberg, Waggoner and Zbinden.[1b] Löwenberg and Zbinden.[1c]

12. (*a*) Notkin, J., and Savitsky, N.: Case of Illuminating Gas Poisoning with a Number of Neuropsychiatric Sequelae, the Main Being Peripheral Neuritis and Parkinsonism, J. Nerv. & Ment. Dis. **74**:293-296 (Sept.) 1931. (*b*) Mackay, R. P.: Neurologic Findings Following Carbon Monoxide Poisoning: Report of a Case, J. A. M. A. **94**:1733-1736 (May 31) 1930.

13. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876-903 (May) 1930.

14. Levine, A., and Schilder, P.: Motor Phenomena During Nitrogen Inhalation, Arch. Neurol. & Psychiat. **44**:1009-1017 (Nov.) 1940.

proceeds sufficiently long for cerebral anoxemia to develop, especially when such contributing factors as anemia and respiratory or cardiac failure are present, it would seem that the anoxemia is the basis for the damage.

According to Barcroft's [15] classification, there are four types of anoxemia: the anoxic, in which the oxygen tension of the blood is low; the anemic, in which the hemoglobin concentration is low; the stagnant, in which the blood flow is diminished, and the histotoxic, in which a toxin prevents the proper utilization of oxygen by the tissues. In our case the hemoglobin concentration preceding the operation was 35 per cent, the oxygen tension of the blood during anesthesia varied from 11 to 15 per cent and the episode of cardiac standstill and apnea lasted about two minutes. There were thus three factors contributing to the cerebral anoxemia. Whether an idiosyncrasy to nitrous oxide contributed a fourth factor we are not prepared to say. Some of our colleagues have told us that they have seen nitrous oxide accidents predominantly in Negroes. The literature does not show any particular susceptibility of persons of this race. Thus, of Courville's [18] 13 patients 3 were Negroes, none of Löwenberg's [11] 10 patients was a Negro and of Caine's [3] 4 patients only 1 was a Negro. The patient whose case was reported by Ford and associates [16] was a Negro, but other scattered reports, such as that by Baldwin,[17] who recorded 14 sudden deaths from nitrous oxide anesthesia and cited many more, did not emphasize any racial predominance.

Our patient, fortunately, recovered, but we should like to postulate the probable location of the lesions. It would seem that the greatest damage occurred in the lenticular nucleus, but that much of this was reversible and was based on edema, which subsided. The cogwheel rigidities were due to damage of the globus pallidus. The decerebrate rigidity and the signs of involvement of the pyramidal tracts show that the long motor tracts were not spared. The definite mental and psychic changes indicate involvement of the cortex. The reason for the relative rarity of choreoathetosis would seem to be that either most patients do not survive long enough to manifest the phenomenon or that when they do the damage to the cortex and pyramidal tracts masks the extrapyramidal effects.

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15. Barcroft, J.: Anoxemia, Lancet **2**:485-489 (Sept. 4) 1920.

16. Ford, F. R.; Walsh, F. B., and Jarvis, J. A.: Case of Extensive Injury to Cerebral Cortex Following Nitrous Oxide-Ether Anesthesia, Bull. Johns Hopkins Hosp. **61**:246-257 (Oct.) 1937.

17. Baldwin, J. F.: Nitrous Oxide-Oxygen, the Most Dangerous Anesthetic, M. Rec. **90**:177 (July 29) 1916.

ASSOCIATION BETWEEN CONVULSIVE SEIZURES AND RHEUMATIC HEART DISEASE

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That heart disease may be of importance in the production of convulsive seizures has been known since the studies by Littré,[1] in 1843. Examples of this association were cited by Kussmaul,[2] Lemoine[3] and Lépine,[4] about 1890, and Gowers' monograph on epilepsy[5] (1885) contains a chapter on this subject. More recently, particularly in the French literature, case reports have appeared under the caption of "cardiac epilepsy."[6]

In an attempt to determine whether rheumatic heart disease is of etiologic significance in the production of seizures, cases in which convulsive seizures and rheumatic heart disease were present in the same

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1. Littré, cited by Oddo, C., and Mattei, C.: L'épilepsie cardiaque, Gaz. d. hôp. **92**:1005 (Oct. 25); 1037 (Nov. 1) 1919.

2. Kussmaul, cited by Oddo, C., and Mattei, C.: L'épilepsie cardiaque, Gaz. d. hôp. **92**:1005 (Oct. 25) 1919.

3. Lemoine, G.: De lépilepsie d'origine cardiaque et de son traitement, Rev. de méd., Paris **7**:365, 1887.

4. Lépine, R.: Sur l'épilepsie congestive à propos du mémoire de M. le docteur Pommay, Rev. de méd., Paris **1**:500, 1881.

5. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Disorders, New York, William Wood & Company, 1885.

6. (*a*) Decourt, J.: A propos de "l'épilepsie cardiaque": Le rôle probable de l'infection rheumatismale et de la chorée de Sydenham dans l'étiologie de certaines épilepsies, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1470 (Nov. 28) 1932. (*b*) Halbron, P.: L'épilepsie cardiaque, Progrès méd. **10**:342 (March 5) 1938. (*c*) Lian, C.: De l'épilepsie cardiaque, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:635 (April 21) 1930. (*d*) Marchand, L.: L'épilepsie cardiaque, Paris méd. **2**:307 (Oct. 16) 1926. (*e*) Mouisset, F., and Gaté, J.: Troubles psychiques, hystéro-épileptiques chez une cardiaque, Rev. de méd., Paris **32**:428 (June) 1912. (*f*) Olmer, D.; Berthier, J., and Olmer, J.: Épilepsie et cardiopathie, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:1750 (Dec. 8) 1930. (*g*) Riser, Planques and Petel: Sur la pathogénie de l'épilepsie cardiaque, ibid. **52**:1242 (July 20) 1936. (*h*) Ramond, L.; Vialard, S., and Gay, G.: Épilepsie cardiaque, ibid. **46**:456 (March 24) 1930. (*i*) Urechia, C. I.: Épilepsie chez une cardiaque, ibid. **47**:851 (May 25) 1931; (*j*) Épilepsie cardiaque chez un sujet atteint de cardiopathie valvulaire, ibid. **48**:1380 (Nov. 7) 1932. (*k*) Vialard, S.: L'épilepsie cardiaque, Médecine **15**:221 (March) 1934.

person were reviewed. Of 2,153 patients with rheumatic heart disease examined during the period from July 1, 1934 to April 1, 1941 in University Hospital, 29 had an associated diagnosis of convulsive disorder. No cases of convulsive disorder were included in this series in which there was any suspicion that cranial trauma, syphilis, alcohol, expanding intracranial lesion, uremia or other epileptogenic factors were of significance in producing the seizures. The Kahn reaction of the blood was negative in all instances, and urinalysis gave normal results unless otherwise specified.

REPORT OF CASES

The cases were grouped according to their relation to the acute rheumatic manifestation. The following cases may be considered as representative of the various groups.

Group 1 (2 Cases).—*Cases in which convulsive seizures preceded onset of the rheumatic fever.*

CASE 1.—F. R., a man aged 26, was in status epilepticus at the age of 5 months and had series of petit mal attacks at the ages of 2, 10 and 17 years. At the age of 21 and 22, respectively, he had attacks of acute rheumatic fever, accompanied by numerous grand mal seizures. Dyspnea on exertion began to appear at the age of 23, and grand mal seizures occurred every three or four days. He had never taken digitalis and gave no family history of migraine, chorea or convulsive seizures.

The neurologic examination revealed nothing significant aside from marked mental deterioration. The heart was enlarged, the rate normal, the rhythm regular and the blood pressure 130 systolic and 80 diastolic. The murmurs associated with aortic stenosis and mitral stenosis were present. The liver was enlarged; the lungs were clear, and there was no edema of the ankles. Roentgenograms of the skull were normal.

Group 2 (3 Cases).—*Cases in which Sydenham's chorea preceded onset of convulsive seizures.*

CASE 2.—G. M., a woman aged 55, had chorea[7] with two pregnancies, at 28 and 30 years of age. At 31 she began to have nocturnal grand mal seizures, which occurred about once a month. At 50 she began to have dyspnea on exertion, a chronic cough and edema of the ankles and took digitalis regularly from this time. She also began to take phenobarbital at this time, and the seizures became less frequent. She gave no family history of migraine, chorea or convulsive seizures.

The results of neurologic examination were normal. The heart was enlarged, the rate normal, the rhythm that of auricular fibrillation and the blood pressure 130 systolic and 90 diastolic. The murmur of mitral stenosis was present; the liver was markedly enlarged, and there was mild albuminuria. There were edema of the ankles and pulmonary congestion on moderate activity, which disappeared with rest. Roentgenograms of the skull were normal.

7. This is assumed to have been Sydenham's chorea because of the later development of rheumatic heart disease.

Group 3 (10 Cases).—*Cases in which there was no history of acute rheumatic fever or chorea.*

CASE 3.—E. C., a white man aged 56, had no cardiac symptoms and gave no history of acute rheumatic fever or chorea. He began to have grand mal seizures at the age of 55 and had thirteen over a period of one and a half years. He had never taken digitalis and gave no family history of migraine, chorea or convulsive seizures.

The neurologic examination gave normal results. The heart was of normal size, the rate normal, the rhythm regular and the blood pressure 116 systolic and 70 diastolic. The murmur of mitral stenosis, confirmed by sound tracings, was present. The lungs were clear; the liver was of normal size, and there was no edema of the ankles. Roentgenograms of the skull and examination of the cerebrospinal fluid gave normal results. An electrocardiogram demonstrated a P-R interval of 0.24 second.

Group 4 (14 Cases).—*Cases in which rheumatic fever preceded the onset of convulsive seizures.*

CASE 4.—A. C., a white man of 32, had acute rheumatic fever at the age of 13; edema of the ankles appeared during the course of the acute joint manifestations, and the patient continued to have symptoms and signs of cardiac decompensation more or less continuously thereafter. Grand mal seizures began at the age of 20. The cardiac symptoms increased markedly at 25, and a diagnosis of constrictive pericarditis was made. He had received digitalis, without benefit, for several periods. He gave no family history of migraine, chorea or convulsive seizures.

The neurologic examination gave normal results. The heart was enlarged; the lungs were edematous; the liver was enlarged; there was free fluid in the abdominal cavity, and edema extended to the sacrum. There were no murmurs. The venous pressure was increased. The rhythm was regular until a two stage surgical removal of the constricting pericardium was carried out. After this procedure auricular fibrillation began, but there was marked improvement in cardiac compensation. With the onset of fibrillation the patient was digitalized. The seizures continued at about the same frequency after operation as before.

CASE 5.—P. G., a man aged 64, had acute rheumatic fever at the age of 25. At 61 he began to have seizures about every three months, characterized by an aura of dyspnea, subjective cardiac irregularity and nausea, which was followed by rigidity and generalized clonic convulsive movements. He had been intermittently under a regimen of rest in bed for the six months preceding examination because of "irregularity of the heart." At the ages of 62 and 63 the seizures occurred about once a month. He had not taken digitalis and gave no family history of migraine, chorea or convulsive seizures.

The neurologic examination gave normal results. The heart was enlarged, the rate 102 per minute, the rhythm that of auricular fibrillation and the blood pressure 165 systolic and 100 diastolic. The murmurs of mitral stenosis and aortic insufficiency were present. The liver was enlarged; there were rales at the bases of the lungs and the ankles were edematous. An electrocardiogram showed auricular fibrillation and marked left axis deviation. The patient was digitalized, but renal and intestinal infarcts developed and death occurred shortly thereafter. Postmortem examination revealed a mural thrombus of the left auricle, recent secon-

darily infected infarcts of the small intestine, anemic infarcts of the right kidney and a fibroblastic deformity of the aortic and mitral valves with myocardial hypertrophy. No abnormalities were observed in the brain.

CASE 6.—R. S., a white man aged 40, had polyarticular rheumatism for six months at the age of 19 and was known to have valvular damage at the age of 20. There was mild dyspnea on exertion, but no other cardiac complaints. At 38 he began to have attacks of loss of consciousness, associated with rigidity and tongue biting, but no clonic convulsive movements were observed. He had never taken digitalis and gave no family history of migraine, chorea or convulsive seizures.

The neurologic examination gave normal results. The heart was enlarged, the rate normal, the rhythm regular and the blood pressure 138 systolic and 86 diastolic. The murmurs of mitral stenosis and aortic insufficiency were present. The liver was of normal size; the lungs were clear, and the ankles were not edematous. Roentgenograms of the skull and examination of the cerebrospinal fluid gave normal results. An electrocardiogram showed a P-R interval of 0.22 second, but otherwise was not noteworthy.

CASE 7.—G. W., a man aged 38, had acute rheumatic fever at the age of 27 and a second occurrence following scarlet fever at the age of 32. Dyspnea and edema of the ankles began after the second attack, and at 34 severe congestive failure, relieved by prolonged rest and digitalis, appeared. At 36 nocturnal grand mal seizures began, occurring every six or eight weeks. The cardiac symptoms were improved with continuous administration of digitalis, but the convulsive seizures were of more frequent occurrence, and the digitalis was not taken regularly. No familial incidence of chorea, migraine or convulsive seizures was reported.

The neurologic examination gave normal results. The heart was grossly enlarged, the rate normal, the rhythm regular except for occasional extrasystoles and the blood pressure 135 systolic and 90 diastolic. There were coarse rales at the base of the left lung; the liver was enlarged, but there was no edema of the ankles. The murmurs associated with mitral stenosis and aortic insufficiency were present. An orthodiagram demonstrated marked cardiac enlargement. An electrocardiogram showed right axis deviation and a P-R interval of 0.28 second.

COMMENT

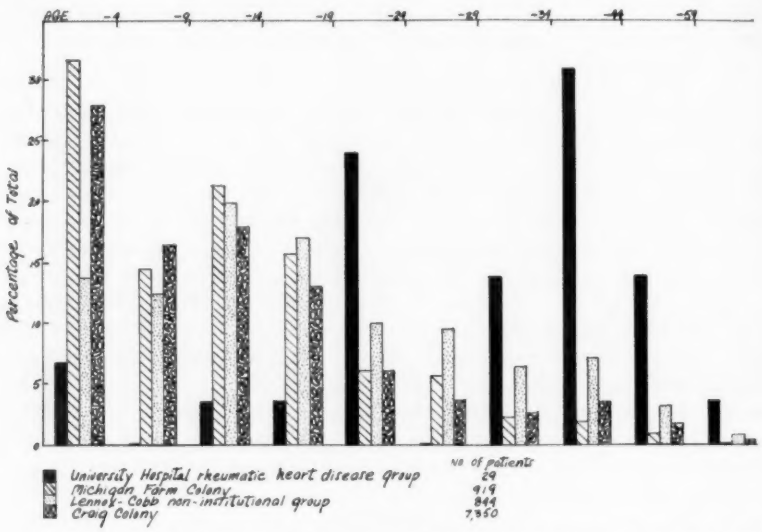
Incidence of Seizures in Rheumatic Heart Disease.—It was estimated by Davenport [8] (cited by Lennox and Cobb [9]) that the incidence of convulsive seizures in the general population was 0.5 per cent. Anderson [10] estimated the incidence of seizures in the general population of the state of Michigan at 0.2 per cent. The patients under consideration were drawn largely from the state of Michigan. Using Davenport's proportion, the anticipated number of patients with seizures among 2,153 patients with rheumatic heart disease is 10.76; using Anderson's figure, the anticipated number of patients with seizures is 4.3. The actual inci-

8. Davenport, C. B.: Ecology of Epilepsy: Geographic and Racial Distribution of Epilepsy, Arch. Neurol. & Psychiat. **9**:554 (May) 1923.

9. Lennox, W. G., and Cobb, S.: Epilepsy, Medicine **7**:105 (May) 1928.

10. Anderson, C. A.: The Incidence of and Related Factors Concerning Epilepsy in Michigan, Ann Arbor, University of Michigan Publications, 1934.

dence of seizures in this group, then, is seven times the expected incidence of seizures in the state of Michigan; taking the higher figure of Davenport, the actual incidence (1.34 per cent) is still more than two and one-half times the expected incidence. Since a goodly number of the 2,153 patients with rheumatic disease were in the early stages of heart disease, this figure is probably too low; 18 of the 29 patients had the onset of seizures after the age of 30, and many of the 2,153 patients have not yet reached the age of 30. It would be necessary to follow the entire group of 2,153 patients until death to obtain the true incidence. These 29 patients represent 1.32 per cent of the total number of patients



Age at onset of seizures in patients with convulsions associated with rheumatic heart disease and with convulsions from all causes.

with convulsive disorders seen in University Hospital during the same period.

Age at Onset of Seizures in Patients with Rheumatic Heart Disease.—The age at onset of seizures for two groups of institutional patients [11] and that for the noninstitutional group of Lennox and Cobb [11a] are compared with the age at onset for our group, and the results are shown in the accompanying graph. As may be seen, there is a distinct tendency for the seizures to appear later in life in patients with rheumatic heart disease than in patients with convulsive seizures of other origin, a point also noted by Oddo and Mattei.[1]

11. (*a*) Lennox, W. G., and Cobb, S.: The Non-Institutional Epileptic, A. Research Nerv. & Ment. Dis., Proc. (1929) **7** (pt. 2):358, 1931. (*b*) Anderson.[10]

Family History of Migraine, Chorea and Convulsive Seizures.—In 20 per cent of the cases there was a familial history of migraine or convulsive seizures. Migraine occurred twice as frequently as seizures among near relatives, a finding which is in keeping with series of more statistical significance than ours.[12] As a control, the family histories in 100 cases of rheumatic heart disease without seizures were reviewed. In this group there were 2 instances of migraine and 1 instance of convulsive seizures among near relatives. This disproportion is compatible with such well known facts as the high familial incidence of seizures in the near relatives of patients with post-traumatic seizures,[11a] for which some factor other than trauma must be postulated to explain the absence of seizures after trauma to the head in a high percentage of cases. The high familial incidence of migraine and seizures in the rheumatic fever group would seem to indicate that the "epileptogenic terrain," the intrinsic ability of the patient to have seizures under the influence of the proper precipitating factor, is important, suggesting that heredity is the basic factor and some manifestation of the rheumatic state the more immediate precipitating influence in seizures. By the demonstration of this high familial incidence it is possible to explain the absence of seizures in the majority of patients with rheumatic heart disease.

Onset of Seizures with Respect to the Acute Rheumatic Manifestations.—In group 1 (2 cases, or 6.8 per cent), in which manifestations of convulsive disorder preceded the rheumatic infection, the rheumatic heart disease can be regarded only as coincidental, of possible importance in increasing the frequency of attacks, but not of fundamental significance in initiating the attacks. In group 3 (10 cases, or 34.4 per cent) no clearly defined history of acute rheumatic fever or chorea was obtained, and the temporal relation of these disorders to the initial convulsive seizure is doubtful. In groups 2 and 4 (17 cases, or 58.6 per cent) the acute rheumatic manifestation clearly preceded the initial convulsive seizure and must be considered a potential factor in the precipitation of the attacks.

Of the 17 cases known to have followed the acute rheumatic manifestation, the onset of seizures came within five years after acute rheumatism in 6 cases, within the period of from five to ten years in 4 cases and within the period of from nineteen to thirty-six years in 7 cases.

Effect of Digitalis on the Convulsive Seizures.—Digitalis has two actions of possible significance in the precipitation of convulsive seizures —it prolongs conduction time from auricles to ventricles, with the production of Adams-Stokes attacks, and it increases the sensitivity of

12. Lennox, W. G.: Migraine and Epilepsy: Newer Concepts and Treatment, J. Med. **19**:284 (Aug.) 1938.

the carotid sinus reflex.[13] In case 7 administration of digitalis preceded the first attack, and the seizures occurred more frequently when the patient was fully digitalized, even though the state of cardiac compensation was much improved with digitalis. The superimposition of digitalis on an already slowed auriculoventricular conduction time (P-R interval 0.28 second) may have been sufficient to cause paroxysmal heart block, with subsequent seizures. In only 1 other patient could administration of digitalis be implicated in the initiation of the first seizure, since only on two occasions had it been given before the first seizure.

As to the effect of the use of digitalis and other measures to improve cardiac compensation on the frequency and severity of the convulsive seizures, the material available does not warrant any conclusions. The improvement in compensation following pericardectomy in case 4 was not accompanied by any improvement in the number of convulsive seizures. Lian [6c] cited 2 cases of rheumatic heart disease with convulsive seizures in which seizures associated with cardiac decompensation disappeared when compensation was regained and reappeared with recurrence of the decompensation, suggesting that the state of compensation is an important factor in the presence or absence of seizures.

Incidence of Decompensation.—There were 17 patients in the series with some evidence of cardiac decompensation at the time of examination, in the form of enlarged heart, enlarged liver, ascites, pulmonary congestion or edema of the lower extremities. It has been suggested that convulsive seizures in persons with heart disease are manifestations of "cerebral decompensation" and that they need not necessarily be accompanied by the more generally recognized evidences of cardiac failure.[14] If "cerebral decompensation" alone is responsible for the seizure, one might expect the patient to be in status epilepticus, because the heart does not decompensate and recompensate in the short period of a petit mal or grand mal attack. The generally recognized evidences of cardiac decompensation were present in some degree in 58.6 per cent of the patients; in this proportion of the total number of patients, then, decompensation producing a disturbance in cerebral physiology may be the precipitating factor in the seizures.

Cardiac Arrhythmia.—"Irritability of the heart is common in chronic valvular disease. Forceful uncomfortable heart beats (in aortic regurgitation particularly), paroxysmal tachycardia, auricular flutter, and auricular fibrillation (paroxysmal or permanent, especially in mitral stenosis), and premature beats and effort syndrome with any of the

13. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, Medicine **12**:297 (Sept.) 1933.

14. Lian.[6c] Vialard.[6k]

valve lesions, are frequently found, but are not essential accompaniments of chronic valvular disease." [15] That paroxysmal cardiac arrhythmia may precipitate convulsive seizures and other cerebral manifestations has been pointed out by a number of authors, including Barnes,[16] Moersch,[17] Smith [18] and Urechia.[6i] It is common experience that paroxysmal cardiac arrhythmia may be completely overlooked at any single examination. The failure to demonstrate paroxysmal cardiac arrhythmias in these cases by no means excludes the possibility of their presence. An abrupt change in rhythm in the permanent arrhythmia, such as transient auricular flutter appearing in permanent auricular fibrillation, may be important in precipitating seizures in the group of patients with permanent arrhythmia. Of the 6 cases with cardiac arrhythmia, 5 were instances of auricular fibrillation and 1 of extrasystole. In 1 instance (case 4) the abnormal rhythm is known to have begun long after the initial seizure; in the other cases the time of onset of the arrhythmia with respect to the inception of seizures was unknown.

Ramond, Vialard and Gay [6h] regarded a prolonged P-R interval in the electrocardiogram as especially significant. They cited an instance of rheumatic valvular disease with a prolonged P-R interval (0.22 second) in a patient with paroxysmal seizures and interpreted the prolonged P-R interval as suggestive of the Adams-Stokes syndrome between the episodes of paroxysmal heart block. In 3 of our cases (3, 5 and 7) the P-R interval was prolonged (0.24, 0.22 and 0.28 second); in case 7 the attacks were more frequent with administration of digitalis. In 4 other cases there were histories suggestive of paroxysmal changes in the cardiac rhythm, but such changes were not positively demonstrated.

Rheumatic Encephalitis.—Decourt [6a] described 5 cases of paroxysmal seizures following Sydenham's chorea and polyarticular rheumatism. Delirium was present in 2 of the cases of acute migratory polyarthritis; in only 1 case were cardiac abnormalities noted. In 3 of the 5 cases the onset of seizures was shortly after the acute rheumatic manifestation. Decourt concluded that "rheumatic encephalitis," expressed either as Sydenham's chorea or in the form of mental symptoms associated with acute migratory polyarthritis, was an important factor in precipitating the type of seizure under consideration.

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15. White, P. D., in Cecil, R. L.: Text-Book of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1934, p. 1147.

16. Barnes, A. R.: Cerebral Manifestations of Paroxysmal Tachycardia, Am. J. M Sc. **171**:489 (April) 1926.

17. Moersch, F. P.: Nervous and Mental Phenomena Associated with Paroxysmal Tachycardia, Brain **53**:244 (July) 1930.

18. Smith, R. T.: Paroxysmal Tachycardia Associated with Epilepsy, M. Press & Circ. **74**:597, 1902.

If cerebral involvement at the time of the acute rheumatic infection is to be implicated directly in the seizure mechanism, one would expect it to bear a reasonable temporal relation to the initial seizure. In only 3 of our 29 cases was there Sydenham's chorea: In 1 case thirty-seven years separated the onset of the chorea from the first seizure; in the second, one year, and in the third, three years. In many of the cases in which joint manifestations were present without chorea, long periods separated the occurrence of the acute joint symptoms and the initial seizure, the longest interval being thirty-six years. That cerebral involvement at the time of the acute infection may be combined with other epileptogenic factors appearing at a later date is a more tenable thesis.

Cerebral Infarction.—Minute emboli passing to the central nervous system, with the production of areas of infarction, have been implicated by Waggoner and Löwenberg-Scharenberg [19] in the production of seizures in patients with rheumatic heart disease. Bruetsch [20] described similar areas of infarction in the brains of patients whose seizures were associated with the rheumatic state, but ascribed the cerebral necrosis to recurrent arteritis of the cerebral vessels. In case 5, in which pathologic examination of the brain was possible,[21] no recent or old emboli were found in the central nervous system, although the immediate cause of death was the dissemination of emboli from an auricular thrombus. Likewise, no changes that could be construed as characteristic of rheumatic encephalitis or rheumatic arteritis were found. In only 1 patient was there evidence from the clinical neurologic examination of embolism of the central nervous system; according to the history the embolic formation occurred four years after the initial seizure. Damage to the central nervous system secondary to subacute bacterial endocarditis [22] was not a complicating factor in any of the cases.

There was no discernible trend in the type of cardiac damage. The incidence of mitral and aortic lesions is high, but not out of proportion to what might be expected in an unselected group of patients with rheumatic heart disease. There were 2 instances of rheumatic heart disease without valvular damage—one with constrictive pericarditis and a second with myocardial damage and no known valvular lesions.

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19. Waggoner, R. W., and Löwenberg-Scharenberg, K.: An Analysis of Certain Brain Pathology Associated with Convulsive Disorders, read at the meeting of the American Psychiatric Association, Richmond, Va., May 5, 1941.

20. Bruetsch, W.: Rheumatic Epilepsy (Sequel of Rheumatic Fever), read at the meeting of the American Psychiatric Association, Richmond, Va., May 5, 1941.

21. The brain was examined by Dr. Konstantin Löwenberg-Scharenberg.

22. DeJong, R. N.: Central Nervous System Complications in Subacute Bacterial Endocarditis, J. Nerv. & Ment. Dis. **85**:387 (April) 1937.

The convulsive manifestations are noteworthy in that there is a distinct tendency for them to appear after the age of 30; in some cases the seizures are of less frequent occurrence than is customary for convulsive seizures of other origin, and a history of cardiac symptoms associated with the seizures appears in some instances.

It should be emphasized that rheumatic heart disease is but one manifestation of the rheumatic state. The possibility that other sequelae of acute rheumatism appearing coincidentally with rheumatic heart disease are operative in the production of seizures is not to be overlooked.

SUMMARY AND CONCLUSIONS

From our material, the following facts may be adduced as evidence that the rheumatic state is of etiologic significance in the production of certain convulsive disorders:

1. The incidence of convulsive seizures in patients with rheumatic heart disease is higher than the incidence in the general population.

2. The age onset of seizures in patients with rheumatic heart disease does not conform to the age onset distribution in the general population.

3. Acute rheumatic fever or Sydenham's chorea preceded the onset of convulsive manifestations in 58.6 per cent of 29 patients; in 34.4 per cent the relation was doubtful, and in 6.8 per cent the convulsive seizures preceded the acute rheumatic infection.

4. A familial incidence of convulsive seizures or migraine appears in the cases of rheumatic heart disease with seizures six times as frequently as in cases of rheumatic heart disease without seizures. This is significant in explaining not only the appearance of seizures in this group but the absence of seizures in the majority of cases of rheumatic heart disease.

The following observations from other sources are corroborative evidence that the seizures are more than coincidental:

1. Cerebral involvement in rheumatic fever in some instances is followed shortly by convulsive seizures, in the absence of heart disease (Decourt [6a]).

2. Improvement in cardiac compensation may be accompanied by amelioration of seizures; cardiac decompensation may be accompanied by exacerbation of seizures (Lian [6c]).

3. Cerebral infarction secondary to cerebral emboli (Waggoner and Löwenberg-Scharenberg [19]) or recurrent "rheumatic arteritis" (Bruetsch [20]) may be associated with convulsive seizures.

Inferential evidence pointing in the same direction is the not uncommon occurrence of paroxysmal cardiac arrhythmia in rheumatic heart disease and the known fact that cardiac arrhythmia may be accompanied by seizures.

The presence of a constant feature in the heart disease which might be considered the sole epileptogenic factor is not demonstrated; that is, not all of the patients had the same valvular lesion, not all had cardiac failure, not all had taken digitalis, not all had permanent arrhythmia, not all seizures followed closely the acute rheumatic manifestations, etc. This is interpreted to mean that there are several mechanisms associated with the rheumatic state capable of producing seizures in predisposed persons: paroxysmal cardiac arrhythmia, passive congestion of the cerebrum, delayed auriculoventricular conduction time, with or without the superimposition of digitalis, cerebral infarction and possibly others.

CORRELATIONS BETWEEN PATTERNS OF BREATHING AND PERSONALITY MANIFESTATIONS

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In 1937 [1] it was suggested that there existed in a series of patients with a diagnosis of schizophrenia a type of breathing which was characteristic of a considerable number of this particular group. Since that time further work has substantiated the observations previously recorded; this paper reports some of the corroborating evidence. It is based on the results obtained from a study of 59 Harvard undergraduates who served as subjects in an investigation by the Grant Study of Social Adjustment at Harvard University, on the observations on a group of Negro share croppers studied in Mississippi and on the measurements derived from 25 patients selected at random from those confined to a hospital for mental disease with a condition diagnosed as chronic schizophrenia.

METHOD

With the subject in a basal state the breathing was recorded on a Roth-Benedict apparatus. From the record thus obtained a representative 100 consecutive inspirations were selected by inspection and their volume measured; the average volume of tidal air and the standard deviation of the values for tidal air were then computed.

The first four minute period of the pneumograph was not included in the process of sampling, since it has been found almost invariably to differ from the remaining portion of the graph; this peculiarity has been attributed to the adjustment of the subject to the incommodity of the apparatus. The record should be at least of twenty minutes' duration in order to insure adequate representation of the subject's breathing pattern. In the large majority of cases the representative sample will be found in consecutive minutes; if, as happened in a few cases, it was felt that a better sample could be obtained by the choice of scattered minute periods, such a choice was made.

The students were seen individually by a psychiatrist for an average of about eight hourly interviews. He subsequently divided the group into three classes: the "schizoid," the "cyclothymic" and a third in which neither schizoid nor cyclothymic elements predominated. It should be emphasized that these terms by no

From the Fatigue Laboratory, Harvard University, Cambridge, Mass., and Metropolitan State Hospital, Waltham, Mass.

1. Thompson, J. W.; Corwin, W., and Aste-Salazar, J. H.: Physiological Patterns and Mental Disturbances, Nature, London **140**:1062 (Dec. 18) 1937.

means necessarily suggest the presence of psychotic manifestations in the students; rather than follow the current lamentable fashion in psychiatry of coining new terms, the words "schizoid" and "cyclothymic" are used to denote the broad types of normal personality sufficiently well known to the general psychiatrist. The measurements of tidal air and standard deviations for this group were arranged in sequence according to magnitude and divided into terciles. Since, as is shown in figures 1 and 2, the patients of the schizophrenic group had a smaller volume of tidal air and more regular breathing than the normal subjects, the

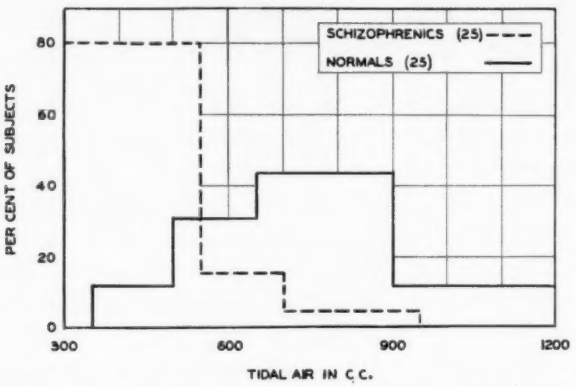

Fig. 1.—Graph showing values for tidal air, expressed in cubic centimeters, for normal and for schizophrenic subjects.

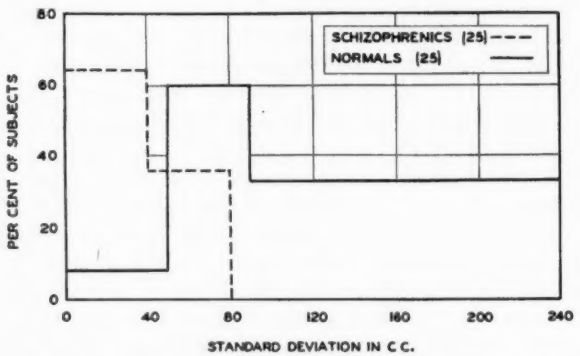

Fig. 2.—Graph showing values for standard deviations of volumes of tidal air, expressed in cubic centimeters, for normal and for schizophrenic subjects.

students pertaining to the lower tercile were termed "schizoid" and those to the upper tercile "cyclothymic." The list of subjects placed under these headings by the psychiatrist was then ascertained and compared with that compiled from physiologic criteria; when the same name appeared under the same heading on both lists, an "agreement" was scored; otherwise, a "disagreement" was scored. The results are shown in table 1. In this table, a third group, "Neurotic Personality," is represented, the members of which showed such psychiatric features

as anxiety attacks, obsessional traits or specific phobias; the pneumograph of such subjects is usually characterized by marked irregularity in breathing, with no discernible pattern. In 5 cases in the entire group the psychiatrist was unable to place the student in one or another of the three categories, the number in which a comparison of this type could be made hence being reduced to 54.

The Negroes formed the material for study on a field trip undertaken by members of the Fatigue Laboratory staff in conjunction with investigators from other laboratories.[2] These subjects were not formally interviewed, although a fair impression of their personalities was obtained as a result of association with them in the course of the other experimental work for which they were subjects.

RESULTS

Reference has already been made to figures 1 and 2, in which are compared the breathing characteristics of 25 schizophrenic patients with those of 25 normal persons. In view of the smaller volume of tidal air, one would expect to find the carbon dioxide content of the patients'

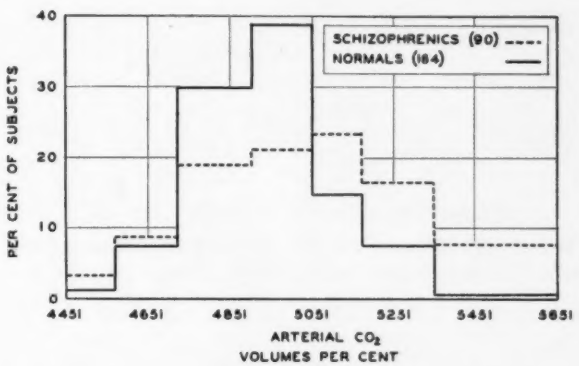

Fig. 3.—Graph comparing values for carbon dioxide content of arterial blood for normal and for schizophrenic subjects.

arterial blood higher than that in the normal group. This, in fact, was found to be the case, as is shown in figure 3, in which are included 65 additional schizophrenic patients. After the completion of these studies it was found in the course of other experiments that in approximately 75 per cent of the patients a premature "starvation ketosis" was prone to develop as a result of having their breakfast withheld. The blood, having been taken with the patient in a basal state for the estimation of carbon dioxide, in all probability contained in some instances fixed acids, so that the figures taken for comparison are not strictly comparable; this additional factor, however, would minimize

2. Dill, D. B.: Fatigue Studies Among Mississippi Share Croppers, Harvard M. Alumni Bull. **14**:1 (Oct.) 1939.

the difference which is indicated. This aspect of the breathing of schizophrenic patients is taken as an example of their generally poor homeostatic mechanism, which we have previously indicated.[1]

TABLE 1.—*Correlation Between Psychiatric and Physiologic Criteria in Normal Subjects (Students)*

	Number	Per Cent
Schizoid (Introvert)		
Agreement	16	80
Disagreement	4	20
	20	
Cyclothymic (Extrovert)		
Agreement	12	75
Disagreement	4	25
	16	
Not Predominantly Either Schizoid or Cyclothymic		
Agreement	12	88
Disagreement	1	12
	13	
Neurotic Personality		
Agreement	5	83
Disagreement	1	17
	6	

TABLE 2.—*Total Volumes of Tidal Air with Means for Five Groups of Subjects*

Series	Number	Range, Cc.	Mean, Cc.	Standard Deviation, Cc.	Coefficient of Variation, Percentage
Benoit, Miss., Negroes...	24	262.14 - 662.13	389.135 ± 10.81	78.50 ± 7.64	20.17 ± 1.96
Bloomington, Ind., Negroes	11	352.48 - 652.47	449.975 ± 14.64	72.00 ± 10.35	16.00 ± 2.30
White workmen, Benoit, Miss.	7	311.10 - 1,361.09	619.095 ± 79.03	310.00 ± 55.88	50.07 ± 9.03
Research group, Benoit, Miss.	10	379.89 - 429.83	504.885 ± 20.80	97.50 ± 14.70	19.31 ± 2.91
Grant Study men.....	59	356.00 - 1,305.00	695.50 ± 16.46	187.50 ± 11.64	26.96 ± 1.67

TABLE 3.—*Standard Deviations of Volumes of Tidal Air for Five Groups of Subjects*

Series	Number	Range, Cc.	Mean, Cc.	Standard Deviation, Cc.	Coefficient of Variation, Percentage
Benoit Negroes.....	24	16.6 - 76.5	38.20 ± 2.03	14.75 ± 1.43	38.61 ± 3.76
Bloomington Negroes...	11	22.8 - 57.7	38.00 ± 2.19	10.75 ± 1.55	29.29 ± 4.07
White workmen, Benoit, Miss.	7	24.4 - 164.3	66.45 ± 10.96	43.00 ± 7.75	64.71 ± 11.66
Research group, Benoit, Miss.	10	29.0 - 118.9	65.95 ± 5.29	24.80 ± 3.74	37.60 ± 5.67
Grant Study men.....	59	37.0- -306.0	99.80 ± 3.66	58.90 ± 3.66	59.02 ± 3.66

Table 1 shows the incidence of agreement in the lists compiled by the psychiatrist and those composed on the basis of measurements obtained from the pneumographs. Tables 2 and 3 compare some of

the breathing characteristics of the Negroes with those of the groups of white subjects. "White workmen" refers to a group of white share croppers living under conditions similar to those of Negroes; "research group" refers to the members of the research staff (all white) who acted also as subjects.

COMMENT

Although there is increasing evidence that the mode of respiration and the general personality of a subject are in some manner related, the difficulty of selecting the essential qualities which bear this relation has by no means been resolved. The depth and regularity of respiration are indicated in this paper as useful criteria; there are undoubtedly others, and almost certainly further study will eventually allow one to select entities more specific than "schizoid" and "cyclothymoid" personalities. No claim whatever is being made for the precision of these psychiatric terms; it can only be maintained that both the patients and the normal subjects, at either extreme, tend to have common properties of two orders: one, the mode of respiration and, second, the ability similarly to influence the examining psychiatrist. In order to emphasize this point, the words "introvert" and "extrovert" have been placed in brackets under the other headings, thus suggesting the lack of certainty which at present is held for the particular entity with which these objective measurements are finding agreement.

That the Negroes as a group have a smaller volume of tidal air and more regular breathing than the white persons in this study is evident. The similarity between the figures for the Benoit and those for the Bloomington Negroes is striking. It seems fair to say that the Negro, by his general passivity, intense imaginative tendencies, amounting often to frank hallucination, religious manias and extensive suspicions and superstitions, tends toward the schizoid rather than toward the cyclothymoid type. If this is so, the findings with respect to respiration in the Negro are in agreement with the argument of this paper.

It seems justifiable to admit the statement that the pattern of a person's breathing bears a useful correlation to some of the characteristics of his "personality." This is not a particularly surprising remark when it is recalled, first, that the term "personality" refers largely to the manner in which a person behaves; his mode of breathing should be no exception. Furthermore, it is a common fact that variations in breathing are frequently associated with specific emotional counterparts: Thus every one is familiar with the alterations in breathing during the experience of joy or sorrow popularly referred to as laughter or weeping, respectively. By an appropriate manipulation of his breathing an actor may leave an audience in no doubt as to the emotion which he is

supposedly experiencing. Any explanation for the occurrence of these associated states, i. e., "mental attitudes" and respiratory patterns, is at present impossible, and indeed will not be forthcoming until some more adequate form of monism than any existing today is achieved. Another, though less formidable, difficulty to be faced in attempting an explanation is the crudity of the data: One is forced to remain uncertain of the personality elements with which the pneumographic measurements are being particularly correlated. Our position could be summarily stated by suggesting that as the pulse yields information regarding the state of the heart, so does the respiration render some information relative to the texture of the personality, and whereas the structure and dynamics of the heart and also its functional relation to the pulse are clear, all the latter information relative to the personality remains to be discovered.

CONCLUSIONS

A type of breathing characterized by a smaller volume of tidal air and greater regularity is found among chronic "schizophrenic" patients more commonly than among normal persons.

The mode of breathing is an index to some of the personality components of normal persons. Those sharing to a greater degree the breathing characteristics common among schizophrenic patients are found frequently to be "schizoid" in disposition.

Suggestive evidence is presented for the existence of racial characteristics in the breathing pattern. These have been demonstrated in races whose personality configurations are also generally distinctive.

INTRASPINAL MENINGIOMAS

A CLINICAL AND PATHOLOGIC STUDY

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Keen and conflicting discussion of the past few years concerning the histogenesis and classification of meningiomas has provided the stimulus for study of 130 such neoplasms arising in association with the membranes of the spinal cord. In the century and a half since Louis,[1] and then Bright [2] and Cruveilhier [3] first described "fungoid and cancerous tumors of the dura mater," knowledge of the life history and cytologic variations of meningeal tumors has been greatly enriched. Although the unproved histogenesis has been an impediment to terminologists, it has stimulated investigation embracing every phase of these tumors; the desire to correlate results has led pathologists at times to study the embryology and comparative pathology,[4] with the result that doubt has been thrown on the specificity of the germ layers.

The comprehensive review of Cushing and Eisenhardt [5] marked all the historical milestones in knowledge of meningiomas, and only specific points that are relative to the current hypotheses require discussion.

This work was done in the Section of Neuropathology of the Mayo Foundation, under the direction of Dr. J. W. Kernohan.

Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurosurgery.

1. Louis: Mémoire sur les tumeurs fongueuses de la dur-mère, Mém. Acad. roy. de chir., Paris **5**:1-59, 1774.

2. Bright, R.: Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy, London, Longman [and others], 1831, vol. 2.

3. Cruveilhier, J.: Anatomie pathologique du corps humain, ou descriptions avec figures lithographiées et coloriées des diverses altérations morbides dont le corps humain est susceptible, Paris, J. B. Baillière, 1829-1842.

4. Vogt, W.: Gestaltungsanalyse am Amphibienkeim mit örtlicher Vitalfarbung: II. Gastrulation und Mesodermbildung bei Urodelen und Anuren, Arch. f. Entwcklngsmechn. d. Organ. **120**:384-706, 1929.

5. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behavior, Life History and Surgical End Results, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

The now confirmed transplantation experiments of Harvey and Burr,[6] designating a leptomeningeal origin from the neural crest, were directly antithetic to the embryologic contributions of Weed,[7] which ten years previously had inferred a mesodermal source for these membranes. The possible relationship between the arachnoid cell and the cell of the sheath of Schwann, as well as the new horizon for the epiblastic parentage of meningioma, neurofibroma and acoustic neurinoma, transcended in importance the immediate application of this work to meningeal tumors alone. In any event, it was apparent to all that in postblastodermic vertebrate embryos there was a close contiguity between migrating neural crest and perimedullary mesenchyme and that at this stage the anlages of pia, arachnoid, dura and periosteum were in such intimate relationship that no further elucidation could be anticipated by the existing embryologic technics. As a result, during the past five years the histogenesis of meningiomas has been attacked through reconstruction and analogy by clinicians and pathologists alike.

The original hypothesis of Cleland [8] that meningeal "cancer" originates in the arachnoid has been confirmed abundantly by the investigations of Schmidt,[9] of Cushing [10] and of Mallory [11] and by the tissue culture work of Buckley and Eisenhardt [12] and of Wolf and Honeyman.[13] Mallory noted the apparent ability of cells of the meningioma to produce collagen and fibroglia and later, supported by Penfield,[14] designated them as undifferentiated fibroblasts; he disregarded both the functional specialization of the arachnoid cell in relation to the cerebro-

6. Harvey, S. C., and Burr, H. S.: The Development of the Meninges, Arch. Neurol. & Psychiat. **15**:545-567 (May) 1926.

7. Weed, L. H.: The Development of the Cerebro-Spinal Spaces in Pig and in Man, Contrib. Embryol. **5**:1-116, 1917.

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13. Wolf, A., and Honeyman, W. M.: A Note on the Appearance of Meningioma in Tissue Culture, Bull. Neurol. Inst. New York **6**:569-573 (Dec.) 1937.

14. Penfield, W.: The Encapsulated Tumors of the Nervous System: Meningeal Fibroblastomata, Perineurial Fibroblastomata and Neurofibroblastomata of von Recklinghausen, Surg., Gynec. & Obst. **45**:178-188 (July) 1927.

spinal fluid and the absence of intraneoplastic reticulin in certain cases reported at that time. In general Oberling [15] and later Cushing,[16] advocated the single, pluripotential "mother cell" doctrine, expressed preference for the neuroectodermal hypothesis and concluded that the hypothetic meningoblast or meningocyte is the sole effector of the multiplicity of histologic patterns which are known today as meningiomas. The existence of this potent morphologic unit was then, and still is, as vague as that of the medulloblast of glial hierarchy. Roussy and Cornil [17] suggested that the meningioma arises from the impotent tissues which are misplaced occasionally in the meningeal membranes during glial migration.

Globus,[18] approaching the problem from the phylogenetic and ontogenetic viewpoint, expressed the opinion that the meningioma is of mesenchymal derivation, arising from the unripe meningeal primordia, which contain the anlage of the mature membranes. The facts that most meningiomas are benign and that the cells of the meningothelial variety (which comprises the largest single subtype) are morphologically identical with mature arachnoid cells weigh strongly against this hypothesis. Ewing,[19] in this connection, expressed the opinion that adult cells do not become embryonal; that dedifferentiation is in truth anaplasia. Foot [20] expressed the opinion, as a result of special staining affinities, that the neoplastic cells are not fibroblasts but are neuroectodermal in origin and stimulate a stroma having fibroblastic and angioblastic potentialities. In a careful analysis of histologic sequences in the meningiomas, Orville Bailey [21] followed a closely allied line of reasoning. Although noncommittal on the subject of embryogenesis, he likewise conceived of these tumors as resulting from a mixture of elements, with the arachnoid cells stimulating an underlying stroma of connective tissue. He confirmed the presence of adult fibroblasts in some specimens; owing to supposed differences in growth rates of the two com-

15. Oberling, C.: Les tumeurs des méninges, Bull. Assoc. franç. p. l'étude du cancer **11**:365-394 (June) 1922.

16. Cushing, H.: The Third Circulation and Its Channels, Lancet **2**:851-857 (Oct. 24) 1925.

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20. Foot, N. C.: Meningiomas, Arch. Path. **30**:198-211 (July) 1940.

21. Bailey, O. T.: Histologic Sequences in the Meningioma, with a Consideration of the Nature of Hyperostosis Cranii, Arch. Path. **30**:42-69 (July) 1940.

ponents, fibroglia was inconspicuous or absent in a third of the cases. The important and long-neglected cervical transplantation experiments of neural crest material performed by Stone [22] showed the striking potentialities of these cells to differentiate into osteoblastic, chondromatous and fibroblastic structures, and are significant in their approach to the different histologic elements occurring in meningiomas.

The thesis therefore is proposed that meningioma is the result of an admixture of two, and at times three, different elements and that the neoplastic cells per se arise from the superficial layer of the arachnoid, particularly in the granulations and other smaller cell clusters, stimulate its stroma, which is likewise of neural crest origin and somewhat less restricted in its growth tendencies, and incorporate mesenchymal elements into the tumor pattern only as a result of the usual rapid adherence of the tumor to the dura for purposes of vascularity. Degenerative changes in the tumor cells, growth alterations of the stroma and these dural components all contribute to the final microscopic picture. Regardless of differences in malignancy, the composite structure in its simplest form is not dissimilar to fibrocarcinoma of the breast or stomach. The only true embryonal tumor of the meninges appears to be the diffuse meningiomatosis of Willis [23] and Weinberger,[24] in which pia or arachnoid or both undergo spontaneous tumefaction, with no recognizable nidus of origin. Diffuse meningiomatosis should be differentiated carefully from both primary sarcoma of the meninges and malignant meningioma.

GENERAL CONSIDERATIONS AND CLASSIFICATION

Intraspinal meningioma arises from the cells of the spinal arachnoid, usually in the region of the arachnoid villi, which lie close to the crossing nerve root. Both Elman [25] and Hassin [26] described these arachnoid tufts minutely; they differed only on the importance of these structures in absorption of fluid and on the question of communication between spinal subarachnoid and perineural spaces. At this "subarachnoid angle" the growth infrequently may adhere to and appear to arise from the crossing nerve root. Surgical description in a large propor-

22. Stone, L. S.: Experiments Showing the Role of Migrating Neural Crest (Mesectoderm) in the Formation of Head Skeleton and Loose Connective Tissue in Rana Palustris, Arch. f. Entwcklngsmechn. d. Organ. **118**:40-77, 1929.

23. Willis, R. A.: A Diffuse Leptomeningeal Tumour in a Child, with Comments on "Sarcomatosis" of the Meninges, J. Path. & Bact. **47**:253-256 (Sept.) 1938.

24. Weinberger, L. M.: Diffuse Meningiomatoses, Am. J. Cancer **38**:1-22 (Jan.) 1940.

25. Elman, R.: Spinal Arachnoid Granulations with Especial Reference to the Cerebrospinal Fluid, Bull. Johns Hopkins Hosp. **34**:99-104 (March) 1923.

26. Hassin, G. B.: Villi (Pacchionian Bodies) of the Spinal Arachnoid, Arch. Neurol. & Psychiat. **23**:65-78 (Jan.) 1930.

tion of cases generally places the meningioma in an extramedullary, intradural location, with adherence to the dura necessitating resection of the involved membrane (fig. 1 *A* and *B*). In this connection Elsberg [27] pointed out that he had observed intraspinal meningiomas at all seven possible locations, inside and outside the three membranes of the cord; he speculated on possible ameboid wanderings of "mesothe-

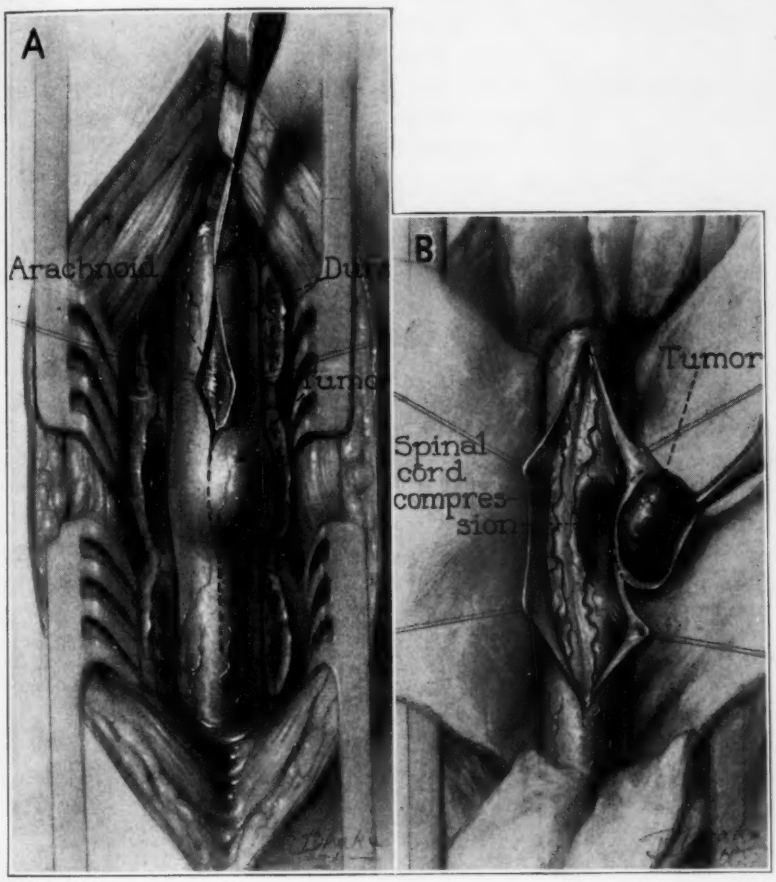

Fig. 1.—Laminectomy. *A*, exposure of the cord, showing intradural location of meningioma and line of incision. *B*, removal of tumor with adherent meninges. (From Adson, A. W.: Intraspinal Tumors: Surgical Consideration; Collective Review, Internat. Abstr. Surg. **67**:225-237 [Sept.] 1938; in Surg., Gynec. & Obst., September 1938).

lial" cells into the dura and pia, as well as the possible incorporation of arachnoid inclusions into the neighboring membranes of the embryo

27. Elsberg, C. A.: Extradural Spinal Tumors—Primary, Secondary, and Metastatic, Surg., Gynec. & Obst. **46**:1-20 (Jan.) 1928.

during the original processes of fusion and splitting. A similar situation has been noted in this series.

It seems likely that inaccurate surgical observation accounts for some of the cases of intraspinal meningiomas. In the process of "shelling out" or piecemeal removal of the growth its attachment to the arachnoid, which is often minute, may be overlooked easily. Mention has been made already of the tendency to early dural attachment as the meningioma grows outward. It may penetrate the dura and become largely extradural, with necrosis or disappearance of the arachnoid pedicle. Pia likewise may be incorporated within the growth, and malignant varieties may cross the pial barrier and actually invade the cord.

A striking difference between meningiomas of the spinal cord and their cranial homologues is the tendency of the latter to hyperostosis. The bones of the cranial vault are known to ossify intramembranously, whereas the vertebral column undergoes intracartilaginous ossification. When cartilage is absorbed in the latter site osteoblastic activity begins from one or several foci, and the process from then on is quite parallel to that in the flat bones of the skull; concomitant production of bone, meanwhile, is proceeding beneath the enveloping periosteum. Ariëns Kappers [28] has pointed out that cranial periosteum should be regarded properly as a layer of dura, but that vertebral periosteum is entirely distinct in origin from spinal dura. Moreover, it is separated from the dura by the fat-filled epidural space. The membrane in truth is originally perichondrium, and to what extent differentiation has served to mask its characteristics can only be surmised. Considering, then, that the hyperostosis results both from the actual penetration of tumor cells into the haversian canals and from the neoplastic stimulation of bone-forming periosteum, and knowing the tendency of meningioma to adhere to, to invade and to stimulate dura, one obtains an inkling of the probable mechanism behind this difference.

The prevailing classifications of meningiomas are based largely on the predominant morphologic characteristics of the tumors. Globus, however, based his classification on the particular cell types and organization present during the embryonic development of the meninges. The considerations previously mentioned have led me to adopt the general morphologic classification following the pattern of Bailey and Bucy [29] and of Cushing and Eisenhardt,[5] with specific exceptions. The grouping has the advantage of being as practical as the simple term "meningioma" itself and follows the trend in terminology of neoplasms in other

28. Ariëns Kappers, C. U.: The Meninges in Lower Vertebrates Compared with Those in Mammals, Arch. Neurol. & Psychiat. **15**:281-296 (March) 1926.

29. Bailey, P., and Bucy, P. C.: The Origin and Nature of Meningeal Tumors, Am. J. Cancer **15**:15-54 (Jan.) 1931.

organs. In the group of 130 meningiomas of the spinal cord, eight different variants have been distinguished: meningothelial, fibroblastic, psammomatous, osteoblastic, lipomatous, chondromatous, melanomatous and, finally, malignant. Meningiomatosis has been separated from these eight types and will be considered in a different category.

The chief omissions immediately apparent are the angioblastic and mesenchymal varieties. Bailey, Cushing and Eisenhardt,[30] in 1928, introduced the angioblastic type as "a meningioma having the usual appearance grossly, which microscopically has the architecture and reticulum of the hemangioblastoma." Three cases were described in detail. In cases 1 and 2 the tumor arose in the substance of the occipital and the temporal lobe, respectively, had no obvious meningeal attachment and pathologically was typical of the cerebellar hemangioblastoma. In case 3 an arteriovenous aneurysm ultimately developed from a vascular tumor of the posterior fossa. This undoubtedly belongs to the group of malformations. Subsequent case reports follow a similar vein, and it appears that the original observation of Cushing and Bailey[31] that hemangioblastoma rarely, if ever, occurs above the tentorium has automatically caused a considerable number of these growths to be classified as angioblastic meningioma. All meningiomas of this series could be termed, to a greater or less extent, vascular tumors, but they were quite distinct from the group of extramedullary hemangioendotheliomas. Classification of the latter as angioblastic meningioma did not seem to be a contribution to terminology.

Similarly, no specimen or part of a specimen corresponded to the mesenchymatous variety of Globus, which, as described, "bears a very strong resemblance to the mesenchymal structure of the meningeal primordium, while in other parts the cellular elements bear a close resemblance to the primitive vascular endothelium." This type was characterized by cellular collections, many blood channels scattered throughout the field, considerable reticulum, regions of liquefaction and foam cells of the Lindau type: a picture strongly suggesting the partially cystic cellular hemangioendothelioma.

Further restrictions were imposed on the other variants. Pure fibromas, osteomas, osteochondromas, chondromas and lipomas were designated as such and were excluded from the series in the absence of the arachnoid type cell as part of the neoplastic picture, despite a meningeal location. The growth of a stroma with, for example, chondromatous potentialities, to the point of outstripping and completely effacing the original neoplastic element, seemed theoretically reasonable but difficult to prove. Intramedullary melanomas and lipomas were excluded

30. Bailey, P.; Cushing, H., and Eisenhardt, L.: Angioblastic Meningiomas, Arch. Path. **6**:953-990 (Dec.) 1928.

31. Cushing, H., and Bailey, P.: Tumors Arising from the Blood-Vessels of the Brain, Springfield, Ill., Charles C. Thomas, Publisher, 1928.

as well on the basis of location. The epithelioid types of Cushing and Eisenhardt,[5] including the "neuroepithelial variety of Roussy," which were characterized as "more undifferentiated meningothelial types," were classed with the malignant varieties.

PATHOLOGIC VARIANTS

Meningothelial Type.—This is the most frequently occurring variety of meningioma (fig. 2 *A*), often bearing no resemblance to the classic

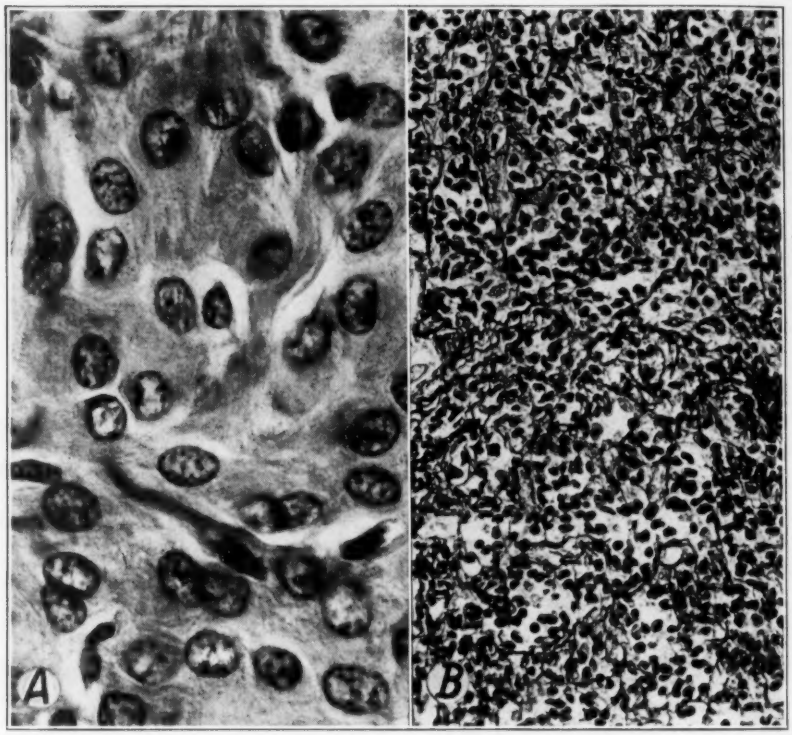

Fig. 2.—Meningothelial type. (*A*) Plump, well nourished cells growing in sheets (hematoxylin and eosin; × 740). (*B*) Small amount of intraneoplastic reticulum (Perdrau stain; × 260).

whorled, calcific tumor that is described commonly. The neoplastic cell is morphologically identical with the superficial lining cell of the arachnoid. The nucleus is elongate, slightly flattened and somewhat vesicular and contains a small amount of chromatin material. The single nucleolus may be seen easily in fresh frozen sections stained with polychrome methylene blue but is inconspicuous or absent in fixed tissue. The cells have a moderate amount of finely granular cytoplasm. When growing in sheets or in the center of a whorl the cells become rounder and in general have a well nourished, or plump, appearance.

Mitotic figures are rare in this variant. Both cell organization and stroma are variable, but there appears to be no practical value in further subclassification. Cell arrangement may be in the form of small islands, sheets, whorls or alveoli. Usually the tumor is moderately vascular, with a good portion of the blood supply entering from the spinal dura. Wavy collagenous fibers and fibroglia in most instances are confined to the stroma about the vessel coats; in a few cases, however, Mallory and Perdrau stains demonstrate a moderate amount of intraneoplastic collagen and reticulum as a result of the inclusion and stimulation of dural components (fig. 2*B*). Adult fibroblasts are visible only in the vessel walls or close by in the periphery of a whorl. These whorls were regarded by Orville Bailey [21] as the expression of the covering tendency of the arachnoid cell with respect to its stroma.

Fibroblastic Type.—The cells of this variety (fig. 3*A*) are more fusiform than the meningothelial cells, at times even spindle shaped. They are arranged in bundles, streams and whorls; the last-mentioned structures tend to hyalinize earlier than they do in meningiomas of the meningothelial type. The pattern is dominated by the collagenous fibers and fibroglia which are interspersed through the tumor, and Penfield [32] has noted the palisading which simulates neurofibroma, owing to the "stream arrangement" of these fibers. Blood vessels are generally sparse, mitoses are absent and psammoma bodies are inconspicuous. In all fibroblastic meningiomas one can identify islands of arachnoid cells, surrounded, compressed and covered in turn by cells resembling fibroblasts: a situation similar to that in the periphery of a whorl. The predominant cell type is derived from the arachnoid stroma, has been stimulated by and then has outgrown the type cell but still attempts to maintain its basic relationship to that cell. Mesodermal elements appear to be negligible in this variant. The pattern is determined by the collagen fibers; one would anticipate the reverse to be true were collagen a secretory product of the tumor cells. This seems to support Masson's [33] conception that collagen is formed from a condensation of the stroma as a result of the influence of these cells, a process which he compared to the clotting of blood.

Psammomatous Type.—Included in the group of meningiomas of this type (fig. 3*B*) were 15 tumors in which the striking histologic feature was the formation of laminated calcareous concretions; any variety, however, may contain these psammomas to a minor extent. Frequently there were contiguous irregular deposits of calcium; however, no specimen showed formation of true bone, a situation quite

32. Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, pp. 953-990.

33. Masson, P.: Experimental and Spontaneous Schwannomas, Am. J. Path. **8**:367-416 (July) 1932.

the reverse of that characteristic of tumors of the osteoblastic variety, all of which showed numerous psammomas. The stroma was plentiful and moderately vascular. The pathogenesis of the corpora arenacea could be followed through varying stages in different fields of a single specimen—whorls of arachnoid cells surrounding a nidus of collagen, elastin or a small thrombosed blood vessel undergo necrosis, hyalinize and then calcify from the nidus outward. For purposes of typing, a criterion of twelve to fifteen concretions per low power field was chosen

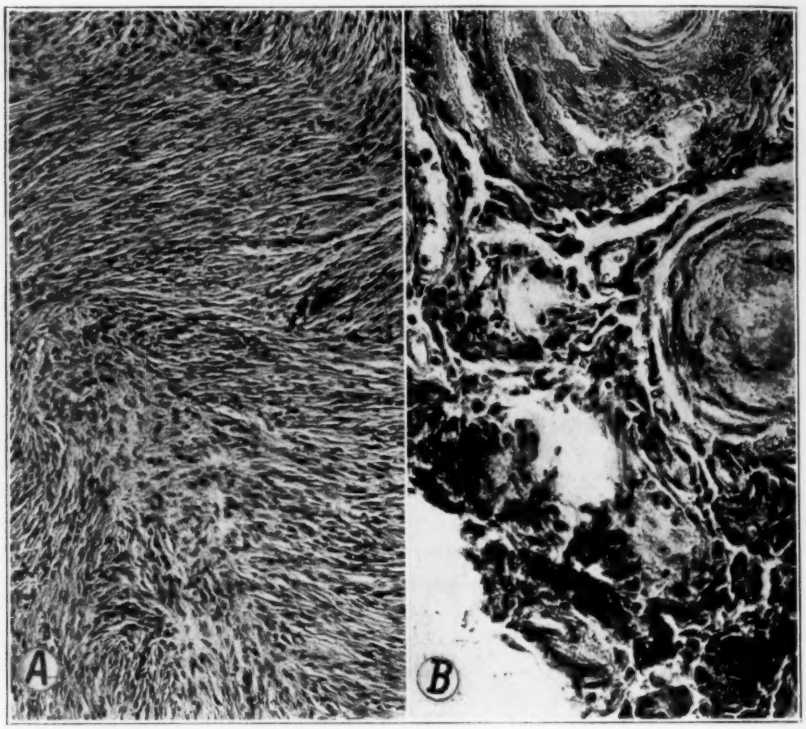

Fig. 3.—(*A*) Fibroblastic type, showing compact bundles of spindle cells of arachnoid stroma surrounding meningothelial islands (hematoxylin and eosin; × 130. (*B*) Laminated concretions of the psammomatous type (Mallory phosphotungstic acid hematoxylin stain; × 260).

arbitrarily to place a tumor in the psammomatous group, and the process, although purely degenerative, will be seen to give rise to a distinctive clinical, as well as histologic, variant.

Osteoblastic Type.—This variety (fig. 4 *A*) was featured by wide zones of mature bone formation, numerous psammomas and occasionally small regions of osteoid tissue and hyaline cartilage. Both Platt [34] and,

34. Platt, J. B.: Ectodermic Origin of the Cartilages of the Head, Anat. Anz. **8**:506-509 (April 27) 1893.

as previously noted, Stone have pointed out the bone and cartilage-forming potentialities of neural crest cells entering into the formation of the gill arches. It seems highly unlikely that dedifferentiation of the specialized arachnoid type cell should occur and result in its transformation into an osteoblast; moreover, transitional phases were not noted. Nests of meningothelial cells situated between the regions of bone and psammoma bodies had stimulated the growth of a stroma with osteoblastic potentialities to the point where it dominated the tumor pattern. Degen-

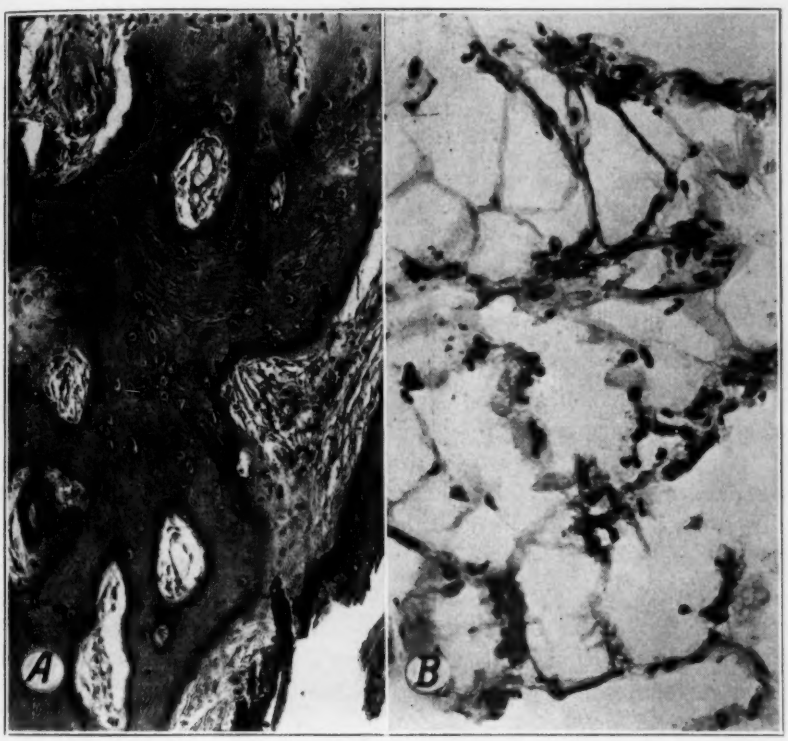

Fig. 4.—(*A*) Osteoblastic type. The bone-forming potentialities of arachnoid stroma cells have outstripped the intervening meningothelial islands (hematoxylin and eosin; × 130). (*B*) Lipomatous type. Fat cells surround tiny nests of the arachnoid type cell (hematoxylin and eosin; × 260).

eration of some regions adjacent to psammomas, with penetration and ossification of these zones by stroma cells, seemed also to be partly responsible for production of bone. This group as a rule was vascularized only slightly, and the small amount of collagen and reticulin was limited to the stroma about the vessels.

Lipomatous Type.—In 2 interesting cases in this series adipose tissue was a prominent feature of the neoplastic process (fig. 4 *B*).

In 1 of them the growth recurred. When removed, the recurrent growth was histologically identical with the original lipomatous meningioma. Both specimens were rather vascular and contained considerable amounts of intraneoplastic and extraneoplastic collagen and reticulin. Typical meningothelial cells comprised a good proportion of the histologic fields, small nests being diffusely interspersed throughout the lipomatous zones. Mitotic figures, again, were extremely scarce. Wells [35] expressed the opinion that adipose tissue is a specialized form of connective tissue and that only cells originally destined for the role become mature fat cells, in this respect resembling glandular organs. Under conditions of new growth, however, this does not seem to be a rigid requirement; it would be difficult to account for such a tumor as lipoma of the corpora quadrigemina or the so-called lipocapsuloma of the kidney under these restrictions. Indeed, it seems quite likely that a variety of cells of mesoblastic origin, when subjected to neoplastic influences, have the propensity of differentiating into mature fat cells. Both tumors of this type in this series were intradural and adherent to the dura and had incorporated dural components.

Chondromatous Type.—In 1 specimen islands of hyaline cartilage were the histologic feature and were associated with easily identified arachnoid cell clusters. The tumor showed several interesting zones in which peculiar hyalinized stroma cells were set in a matrix that stained with hematoxylin; these zones were thought to be representative of transitional cells. The growth was vascularized only slightly and contained a few psammomas, in addition to cartilage. The histologic picture expressed the influence of meningothelial cells on a stroma having chondroblastic potentialities.

Melanomatous Type.—There was 1 melanomatous meningioma (fig. 5 *A*), which arose in the leptomeninges and became adherent to the intradural portion of a posterior root. Schnitker and Ayer [36] have reviewed reports of 30 primary melanomas of the brain and cord, most of which were highly malignant. However, Ray and Foot [37] recently reported 2 cases of a benign variety with no evidence of recurrence or metastasis to date and chose to distinguish between this pigmented form without mitotic figures or nerve fibrils and the truly malignant melanoma. The anlage of growths of the melanomatous type is accepted generally to be the melanoblasts of the leptomeninges, which are found

35. Wells, H. G.: Adipose Tissue, Neglected Subject, J. A. M. A. **114**:2177 (June 1); 2284 (June 8) 1940.

36. Schnitker, M. T., and Ayer, D.: The Primary Melanomas of the Leptomeninges, J. Nerv. & Ment. Dis. **87**:45-73 (Jan.) 1938.

37. Ray, D. S., and Foot, N. C.: Primary Melanotic Tumors of the Meninges: Resemblance to Meningiomas; Report of Two Cases in Which Operation Was Performed, Arch. Neurol. & Psychiat. **44**:104-117 (July) 1940.

normally about the base of the brain and the sulci of the spinal cord. Ewing has strongly supported their neuroectodermal origin, and his reasoning is additional support for the neural crest hypothesis. The tumor in this series was composed of large vesicular epithelial cells with one or more prominent nucleoli. The cells were arranged in cords and occasionally in whorls, with many coarse, pigmented granules in the abundant cytoplasm. These granules showed an affinity for silver

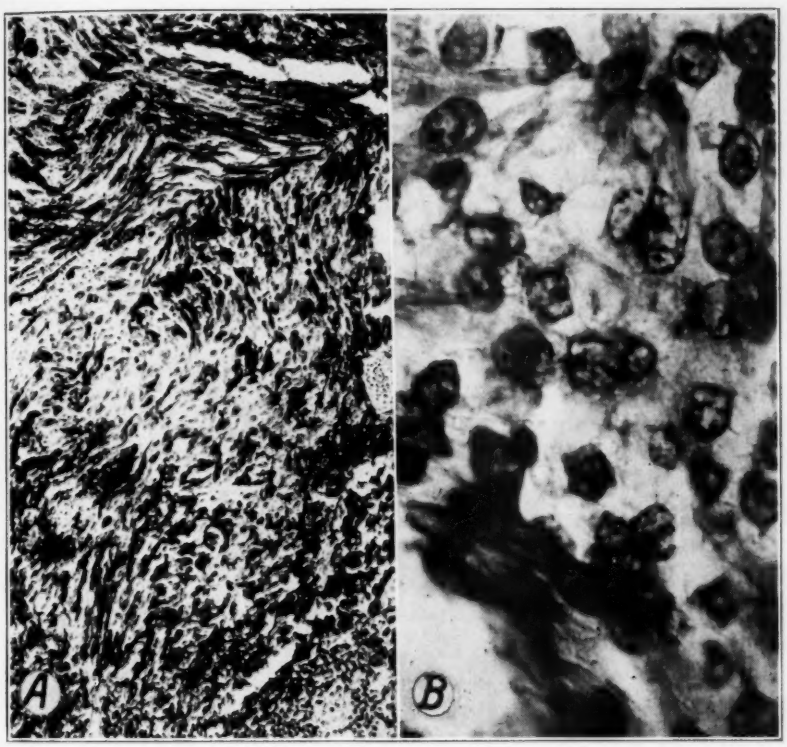

Fig. 5.—(*A*) Melanomatous type, with massive impregnation of pigment with Becker's silver stain (× 130). (*B*) Malignant type, showing hyperchromatic nuclei, foam cells and giant cells with mitotic division (hematoxylin and eosin; × 740).

stains and were negative for iron. Mitoses were not numerous. There were wide regions of hemorrhage and necrosis, with phagocytosis of pigment. The origin, cell type and tumor pattern were all compatible with a diagnosis of malignant meningioma except for the melanin content of the cytoplasm.

Malignant Types.—The 6 tumors of the malignant type were characterized by large vesicular cells, and often by foam cells, having a

single prominent nucleolus (fig. 5 *B*). Epithelioid cells, and at times giant cells, also were observed. Mitotic figures were more numerous than in the meningothelial type. Growth in 2 instances was in the form of cords of epithelial cells partitioned off by the stroma into alveolar formations. Wide zones of hemorrhage within the tumor were noted commonly. The cell type was characteristic of the meningothelial variety which had undergone a moderate anaplastic change. The histologic features in general correlated with the criteria of malignant change in the meningioma as outlined by Craig.[38]

CLINICAL FEATURES

In 1940 Rasmussen, Kernohan and Adson,[39] in their report on intraspinal tumors, noted the frequency of meningiomas to be 25 per cent, second only to the incidence of neurofibromas. It was felt that the importance of these neoplasms warranted a detailed clinical study

TABLE 1.—*Distribution of One Hundred and Thirty Intraspinal Meningiomas*

Location	Cases	Per Cent
Cervical	24	18
Thoracic	101	78
Lumbar *	3	2
Lumbar †	1	1
Lumbosacral	1	1
Sacral	0	0

* Above the termination of the spinal cord.
† Below the termination of the spinal cord.

in order to correlate the life histories of the different pathologic variants and to determine what generalizations would be of diagnostic and prognostic significance.

The distribution of meningiomas at the different levels of the spinal cord is given in table 1. It will be noted that 78 per cent occurred in the thoracic segments, while only 2 tumors in the series were situated below the termination of the spinal cord. Although the incidence of meningiomas in the latter location is somewhat higher in other reported series, for practical purposes meningioma may almost be disregarded in the diagnosis of tumors of the cauda equina. Figure 6 depicts the individual distribution and shows more strikingly the midthoracic preponderance. In the greatest single number of cases, 19, the tumor occurred at the level of the eighth thoracic segment.

38. Craig, W. McK.: Malignant Intracranial Endothelioma, Surg., Gynec. & Obst. **45**:760-768 (Dec.) 1927.

39. Rasmussen, T. B.; Kernohan, J. W., and Adson, A. W.: Pathologic Classification, with Surgical Consideration, of Intraspinal Tumors, Ann. Surg. **3**:513-530 (April) 1940.

Table 2 shows the incidence of the eight varieties and the average preoperative duration of symptoms for each. It is important to note that the meningothelial type comprises more than half of the total number and that the combined meningothelial and fibroblastic types, the so-called parenchymatous varieties, make up 77 per cent of the total. The malignant type has an incidence of 5 per cent, a figure similar to that for the malignant intracranial meningioma, although various estimates of the latter reach as high as 10 per cent. With respect to the average preoperative duration of symptoms for the whole series, which was twenty-three months, it is interesting to observe the increase over this figure for the calcific psammomatous and osteoblastic types and the decrease for

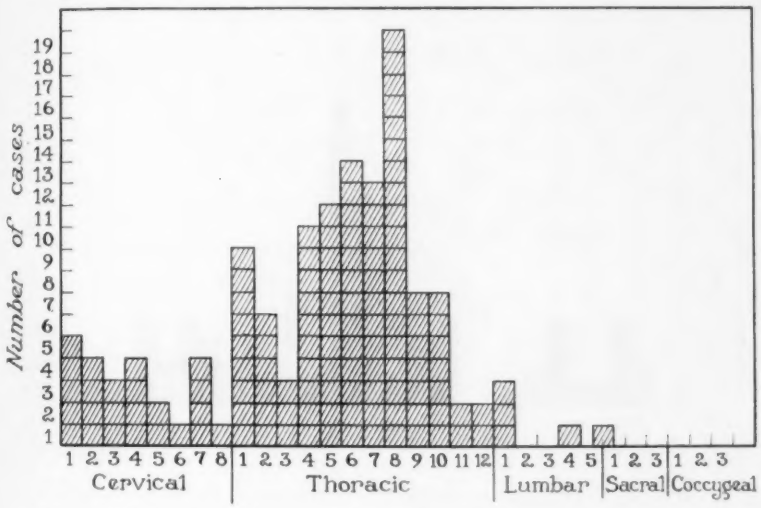

Fig. 6.—Individual segmental distribution of 130 intraspinal meningiomas.

TABLE 2.—*Incidence of the Eight Varieties and Their Average Preoperative Duration of Symptoms*

Type	Incidence		Average Preoperative Duration of Symptoms, Months
	Cases	Per Cent	
Meningothelial	73	56	22
Fibroblastic	28	21	22
Psammomatous	15	12	29
Osteoblastic	4	3	36
Lipomatous	2	3	..
Chondromatous	1		..
Melanomatous	1		..
Malignant	6	5	13
Total for all types	130		23

the malignant type; no conclusion is warranted with respect to the other rare variants. However, it must be realized that all types show extreme variations from this average; figure 7 points out the individual deviations

in duration of symptoms for the rapidly growing malignant form and for the more slowly growing psammomatous type. In only 3 of the group of 15 cases of the latter type was the duration of symptoms actually greater than the general average duration of twenty-three months. In their analysis of tumors of the cervical portion of the spinal cord, Craig and Shelden [40] commented on the relative rapidity of onset of intraspinal as compared with intracranial meningioma and pointed out that neurofibroma of the cord has a longer average preoperative duration than meningioma, despite the expectation that a patient who has neurofibroma would seek relief from root pain earlier.

Table 3 illustrates the chief presenting symptoms for which the 130 patients sought relief. It is noteworthy that a varying degree of motor

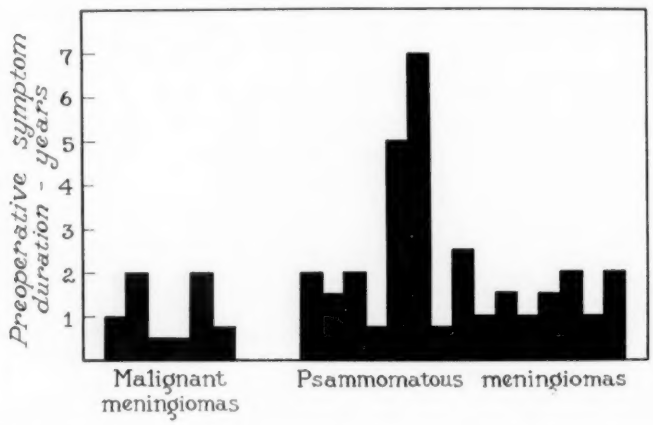

Fig. 7.—Individual duration of preoperative symptoms for the malignant (6 cases) and the psammomatous type (15 cases).

weakness of the arms or legs was considerably more frequent than complete paralysis of one or more extremities, and that 106, or more than 80 per cent, of the patients arrived with considerable motor deficit. Paresthesias, in the form of prickling, stinging and burning sensations, generally in the lower extremities, were prominent in 52 patients and usually antedated the onset of motor weakness. It is significant that although root pain occurred at some time or other in practically every case, it was a main concern of only 51 patients. Loss of sensation, subjectively noted in the thermal sphere in most cases, was a chief complaint of 42 patients. Despite the long preoperative duration in some cases, none of the patients were concerned particularly with

40. Craig, W. M., and Shelden, C. H.: Tumors of the Cervical Portion of the Spinal Cord, Arch. Neurol. & Psychiat. **44**:1-16 (July) 1940.

atrophy. This fact is perhaps a testimonial to the amount of compression that the cord can endure with only negligible destruction of the anterior horn cells and axons. Nineteen patients complained of localized pain in the back without characteristic radicular extension; this was associated with vertebral tenderness on percussion and roentgenographic evidence of erosion of the pedicles. It is interesting to observe that urinary incontinence was approximately twice as frequent as weakness of the detrusor mechanism of the bladder, an observation that one could almost infer from the predominantly thoracic location of these neoplasms. Painful involuntary spasms, generally in the legs, accompanied by a typical mass reflex, were a feature in 9 instances.

TABLE 3.—*Frequency of Chief Presenting Symptoms in the Eight Varieties of Meningioma*

Chief Presenting Symptoms	Total Frequency	Variety							
		Meningothelial	Fibroblastic	Psammomatous	Osteoblastic	Lipomatous	Chondromatous	Melanomatous	Malignant
Motor weakness (arms or legs)	75	43	15	9	2	1	0	1	4
Paresthesias	52	31	12	5	1	1	0	0	2
Root pain	51	31	10	6	0	0	1	1	2
Subjective sensory loss	42	24	7	6	2	1	0	0	2
Ataxia	37	22	7	6	1	0	0	0	1
Complete paralysis (arms or legs or both)	31	16	8	3	2	0	1	0	1
Incontinence (bowel; bladder)	31	12	10	4	3	1	1	0	0
Localized pain in back	19	11	4	2	0	0	0	1	1
Difficulty in voiding; constipation	16	9	5	2	0	0	0	0	0
Spasticity	12	7	1	2	0	0	0	0	2
Muscle spasms	9	4	3	1	1	0	0	0	0
Total number of cases *	130	73	28	15	4	2	1	1	6

* As there may be more than one symptom in a given case, the sum of the items in a column does not equal the total number of cases given at the foot of the column.

This study of the symptoms of these patients unfortunately in no way designates the type of pathologic change in any particular case, and one must concede that in most instances the clinical diagnosis is no more specific than that of extramedullary, intraspinal tumor. However, at times the probable nature of the neoplasm may be inferred before operation by utilizing available experience of its behavior and life history, particularly in contradistinction to the neurofibroma, which, with the meningioma, comprises the great bulk of extramedullary tumors. It has been noted that preoperative duration of symptoms varies with type in the direction that one might anticipate, but in general averages somewhat less than that of the neurofibroma group. Moreover, the average age of these 130 patients was 51 years, or about 10 years greater

than that of the neurofibroma group. Analyses of spinal fluid have not been of any differential aid; roentgenographic evidence, however, is considerably more helpful. About 4 per cent of the osteoblastic and psammomatous tumors will calcify sufficiently to be visible roentgenographically. Furthermore, about 45 per cent of all intraspinal neurofibromas will produce demonstrable bony erosion (especially with enlargement of the intervertebral foramen in cases of the dumb-bell variety), as against only 10 per cent for all types of meningioma. Estimates of the gross bulk of tumors of both types within the spinal canal over a period of years indicate that on the average meningiomas are considerably smaller at the time of operation. Studies made with air and radiopaque oil tend to bear this out by showing partial or complete block to be more prevalent in the neurofibroma group.

To summarize, then, when there are the signs and symptoms of an extramedullary tumor of the cord and when the patient is 40 years of age or less, with a clinical history of symptoms of two and a half to four years' duration, the presence of a noncalcifying, bone-eroding neoplasm giving evidence of blockage in the spinal subarachnoid pathways tends to favor the diagnosis of neurofibroma; similarly, when the clinical syndrome can be established with reasonable certainty in the absence of block or demonstrable roentgenographic bone change, when the patient is 50 years of age or more and when the symptoms extend back over a two year period or less, one may anticipate finding a meningioma with a fair degree of accuracy, more particularly in cases of those rare variants in which there is visible calcification.

REPORT OF CASES

The basis for the division of meningiomas into eight pathologic variants and for the acceptance of the neural crest hypothesis, as presented in this report, rests entirely on an analysis of my own available material, with a critical examination of the literature as a background. For this reason, mention has been made that a considerable number of tumors which failed to satisfy all criteria of origin, location, cytologic character and neoplastic pattern were excluded, although it is likely that many of these were in truth meningiomas. The following case report illustrates this.

CASE 1.—A 61 year old man was admitted with a four year history of steadily increasing weakness, incoordination and paresthesias of the left leg. Examination revealed paresis, hyperreflexia and hypertonia of the left lower extremity, with hypesthesia and thermal loss in the right lower extremity—that is, an incomplete Brown-Séquard involvement. Lumbar puncture showed a questionable partial block, a total protein content of 100 mg. per hundred cubic centi-

meters, a negative serologic reaction with midzone type of colloidal gold curve and a normal cell count. Roentgenologic studies revealed nothing significant. The clinical impression was that the lesion was a lumbosacral tumor of the cord. Laminectomy revealed an intramedullary tumor of the lower lumbar portion of the cord; on dorsal incision a brownish black, friable, semiencapsulated tumor mass extruded, and subtotal extirpation was carried out. Postoperative convalescence was uneventful. Definite signs of recurrence with no evidence of metastasis outside the central nervous system supervened four years later, and at the last report the patient was receiving palliative radiation. Microscopically the tumor cells were typically arachnoidal except for a somewhat more prominent nucleolus and were patterned into the streams and whorls characteristic of meningioma. Mitoses were not abundant. The cytoplasm of many cells contained masses of coarse brownish pigment granules, which were impregnated with Becker's silver stain but were negative to the ammonium sulfide-potassium ferrocyanide reaction for iron. Intraneoplastic collagen or reticulin could not be demonstrated with Mallory stains; specimens stained for mucin were likewise negative.

This tumor apparently arose in the leptomeningeal extensions accompanying the blood vessels into the sulci of the cord (where chromatophores were particularly abundant) and had crossed the pial barrier to acquire an intramedullary location. Despite the plausibility of this theoretic reconstruction it was thought best to exclude this case from the series at present on the basis of situation and to classify it simply as an intramedullary melanoepithelioma.

The tumor in this case provides an excellent contrast to a single melanomatous meningioma which was located intradurally at the fourth servical segment and within four months metastasized widely throughout the cerebrospinal axis and to the liver. In this connection, Schnitker and Ayer have reported 4 cases (including their own) of primary melanomatous tumor of the central nervous system metastasizing to the liver, lungs and spleen, and this, to my knowledge, is the fifth.

The great bulk of intraspinal meningiomas, however, have a more encouraging prognosis. The following case report of a meningothelial tumor is representative of this group.

CASE 2.—A 45 year old woman was admitted with a history of pain, ataxia and increasing weakness of the lower extremities for two years. Eight months before admission to the hospital root pain had been interpreted elsewhere as gallbladder disease and cholecystectomy had been performed. Soon after this complete paralysis supervened and sphincteral control was lost. Four months prior to admission thoracic laminectomy was performed elsewhere, with negative results. Physical examination on admission showed paralysis, spasticity and exaggerated reflexes in the lower extremities. There was slight loss of vibratory and tactile sensation in the legs but no definite sensory level. Lumbar puncture showed normal pressure with a complete block, a total protein content of only 30 mg. per hundred cubic centimeters but a positive Pandy reaction, a normal cell count and a negative serologic reaction with a midzone type of colloidal gold curve. Radiopaque oil revealed a definite block at the level of the first thoracic vertebra.

Laminectomy revealed an encapsulated tumor, 1.7 cm. in length, lying intradurally, adherent to both arachnoid and dura at the level of the second thoracic segment; complete removal was carried out. At the time of discharge motion had returned to the left foot and toes. Improvement continued at home, and when the patient returned after two years for reexamination there was full restoration of motor power, gait was normal, sphincter control had been regained and pain in the legs had practically disappeared. She was seen ten years later for treatment of menopausal symptoms and again was found to be neurologically normal.

For many years the literature has contained confusing reports of diffuse and widely seeded tumors of the meninges. It now seems quite clear that glial, sarcomatous or meningeal cells may participate in this process. Moreover, one can differentiate isolated glioma arising in heterotopic tissues, as has Orville Bailey,[41] from gliomatosis occasioned, for example, by medulloblastoma; mixed or spindle cell sarcoma from sarcomatosis of the meninges, as reported by Cassirer and Lewy,[42] and single or multiple meningiomas, including the melanomatous variety, from the meningiomatosis of Weinberger and generalized melanomatosis. The first two varieties invariably will show a focal origin if examined carefully, but meningiomatosis will not. It is important to categorize such tumors clearly into one of these classes whenever possible in order to avoid confusion in terminology and the use of such loose terms as "sarcomatosis of the meninges" and "sarcomatous meningioma" when one is describing epithelial neoplasms. Diffuse meningiomatosis warrants consideration in this report as an embryonal tumor arising in leptomeninges which have been arrested in development; it forms a diffuse tumor opacity over the brain and cord, which on gross inspection may be mistaken for an exudate. The clinical course is usually one of chronic meningitis. The process is a tumor transformation, and as a result it may be impossible to identify the leptomeninges microscopically. The following case is illustrative.

Case 3.—A 23 year old man was admitted with a five month history of difficulty in voiding and pain, fluctuating weakness and paresthesis of both lower extremities. Clinical findings consisted essentially of flaccid paralysis, hyporeflexia and hypesthesia of the legs, a poorly defined sensory level at the twelfth thoracic segment and bilateral papilledema of 3 to 4 D. The tentative diagnosis was tumor of the posterior fossa with metastasis to the cord. Before further investigation could be begun, signs of meningismus developed; the patient became restless, disoriented and comatose and died of respiratory failure one week after admission. Necropsy did not reveal anything abnormal in the viscera. The spinal cord was surrounded by a diffuse cuff of hemorrhagic tumor from the lower cervical region down to and including the cauda equina (fig. 8 *A*). From the cervical portion of the cord to the cerebrum there were isolated opacities in the leptomeninges representing small collections of tumor, but no separate neoplastic nodules. A small amount

41. Bailey, O. T.: Relation of Glioma of the Leptomeninges to Neuroglia Nests, Arch. Path. **21**:584-600 (May) 1936.

42. Cassirer, N., and Lewy, J., cited by Ewing.[19]

of blood was present in the subarachnoid space and the ventricles, and the latter showed slight uniform dilatation. Microscopically the tumor was composed of large oval and polyhedral cells, having a single nucleolus and a moderate amount of clear cytoplasm which stained feebly with eosin (fig. 8 *B*). Mitotic figures were remarkably scarce. The growth was vascular, and the Mallory phosphotungstic acid hematoxylin stain showed a considerable amount of reticulin in the stroma. No fibers were distinguished in Weigert preparations. The tumor occupied the pia and arachnoid and extended along the perivascular sheaths; in most sections only the superficial layer of arachnoid could be identified clearly.

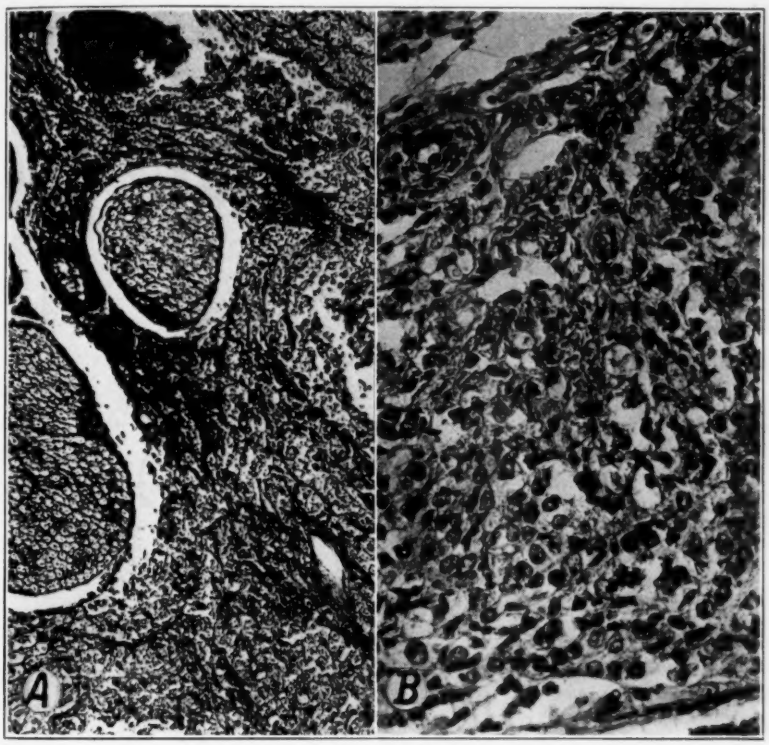

Fig. 8.—Diffuse meningiomatosis. (*A*) A cuff of hemorrhagic tumor surrounds the posterior root fibers (Mallory-Heidenhain stain, × 130). (*B*) The pia-arachnoid is transformed into a tumor mass, and the meningeal landmarks are obliterated (hematoxylin and eosin; × 260).

The features of this case, then, are the continuous conversion of the leptomeninges into neoplasm from the lower cervical region down, scattered transformation above this level, no discernible solitary focus of origin and obliteration of the architecture of the deeper layers of arachnoid and of pia. The cells did not appear highly malignant, and mitoses were infrequent, as were giant cells; they were fairly uniform

in appearance and seemed moderately undifferentiated but not anaplastic. The whole picture made spread or metastasis from any primary source highly unlikely.[43]

SUMMARY

Meningioma is the product of an admixture of elements—the specialized arachnoid type cell, its multipotential stroma and at times dural components as well. The tumor is of neural crest origin, and its only mesoblastic structures are a result of dural attachment. One hundred and thirty intraspinal meningiomas have been classified into eight types. Each tumor has been examined both clinically and pathologically. Diffuse meningomatosis, the neoplastic transformation of embryonically arrested leptomeninges, has been delineated in a separate category and differentiated from gliomatosis, sarcomatosis and melanomatosis of the meninges.

43. To my knowledge no analogous tumor has been observed in any other organ of the body.

SECTION OF THE SPINOTHALAMIC TRACT AT THE LEVEL OF THE INFERIOR OLIVE

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AND
JAMES L. O'LEARY, M.D.
ST. LOUIS

The literature concerning the pain pathways in the central nervous system and their surgical interruption for the alleviation of pain has been extensively reviewed.[1] The present communication adds direct observations which concern the localization of the pain fibers from the body at the level of the inferior olive and confirmatory data on the course of the spinothalamic tract through the brain stem.

The technical procedure of interrupting the spinothalamic tract in the medulla, resulting in relief of high, intractable pain on the opposite side of the body, has been described in an earlier report.[2] On the basis of the sensory changes noted during the operation, it was concluded that a topical arrangement of fibers is present within the spinothalamic tract, so that at the level of the inferior olive fibers belonging to the lower dermatomes of the body lie more superficially while those of the upper ones occupy a more medial position. This arrangement is generally similar to that which has been reported previously for the spinothalamic fibers in the cord.[3]

We have had a second opportunity of performing intramedullary section of the spinothalamic tract for the relief of high, intractable pain and were again able to correlate sensory changes in different parts of the body with increasing depth of incision. After the operation, the patient was completely free of pain until her death from carcinoma, a

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1. (*a*) Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1-92, 1931. (*b*) Walker, A. E.: The Spinothalamic Tract in Man, Arch. Neurol. & Psychiat. **43**:284-298 (Feb.) 1940. (*c*) Grant, F. C.: Surgical Methods for the Relief of Pain, J. A. M. A. **116**:567-571 (Feb. 15) 1941.

2. Schwartz, H. G., and O'Leary, J. L.: Section of the Spinothalamic Tract in the Medulla with Observations on the Pathway for Pain, Surgery **9**:183-193, 1941.

3. Foerster and Gagel.[1a] Walker.[1b]

month later. The length of the postoperative survival period permitted satisfactory studies of the brain by the Marchi method. This gave much additional information concerning the course of the fiber tracts interrupted by the incision.

REPORT OF A CASE

History and Examination.—The patient, an unusually intelligent and cheerful white woman, aged 46, was admitted to the surgical service of the St. Louis City Hospital on Sept. 16, 1940, complaining of pain in the right shoulder, scapular region and thigh. A diagnosis of carcinoma of the breast with metastases to the axilla was made. Preliminary roentgen therapy was advised, and a complete course was given.

Pain in the right side of the chest, right shoulder and upper portion of the right arm became increasingly severe. Morphine was given to the point where there were marked pupillary constriction and frequent vomiting. A neurosurgical consultation was requested on Dec. 7, 1940 to determine the procedure best adapted for alleviation of the pain. Examination on that date revealed, in part, pinpoint pupils and a nonpainful pathologic fracture of the left hip. A large, firm, immobile mass was present in the outer quadrant of the right breast and another mass in the anterior axillary fold. Roentgenograms of the chest were inconclusive with regard to pulmonary involvement. Section of the left spinothalamic tract in the medulla was decided on.

Operation (Dec. 9, 1940).—With the use of local anesthesia a left unilateral suboccipital craniotomy was performed. The technic was essentially the same as originally described.[2] The occipital bone was removed on the left side to the roof of the foramen magnum. After opening the dura and evacuating the fluid in the cisterna magna and left cisterna lateralis, the tonsil and posterior part of the left cerebellar hemisphere were retracted upward, exposing the left lateral wall of the medulla (fig. 1). The ninth, tenth and eleventh cranial nerves were identified. The posterior inferior cerebellar artery in this patient differed from the one found in our first case [2] in that it lay free and well away from the brain stem. The bulbar portion of the accessory nerve was separated from the rootlets of the vagus nerve, exposing the lower portion of the olivary eminence. An incision was then made between the vagus and the olive in a medial and slightly dorsal direction (fig. 3*A*). As the incision was deepened, examination showed analgesia beginning in the right foot and progressing upward to the groin. Finally, at an incisional depth of about 5 mm., analgesia was demonstrable to the shoulder. At this point the patient stated she was free of pain; accordingly there was no need to extend the incision. Cutting the spinothalamic tract was not accompanied by pain. The wound was closed in layers with silk sutures. At the end of the operation the right pupil was very slightly larger than the constricted left pupil. There was no sensory deficit in the trigeminal distribution. Some nystagmus was present on lateral gaze, with a quick component to the right. Speech was intact, and there was no difficulty in swallowing.

Course.—The postoperative course was uneventful. On the night of operation the temperature rose to 103.2 F., from which peak it promptly fell to normal. The pulse and respirations remained normal. The blood pressure had not changed

in comparison with the normal preoperative pressure. There was no "progressive confusional state," as reported by Putnam [4] in some cases of high cervical lesions. Figure 2 shows the results of postoperative sensory examination which was checked

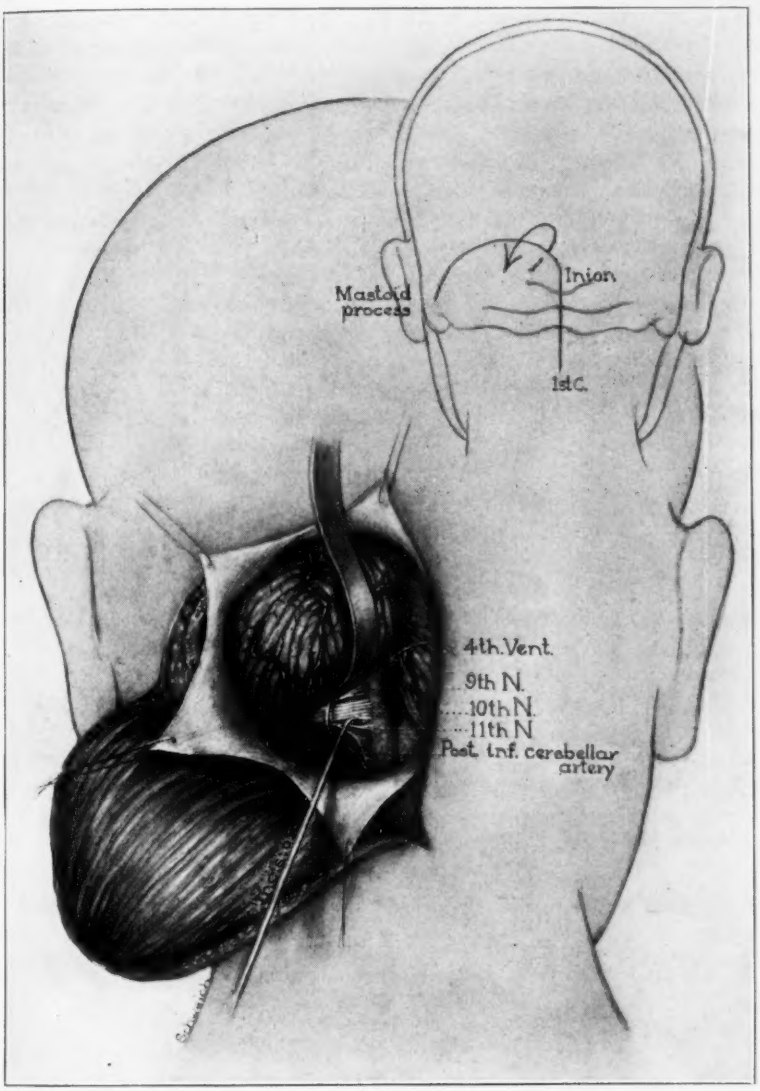

Fig. 1.—Exposure of the left lateral wall of the medulla for section of the spinothalamic tract. The knife point is directed between the rootlets of the vagus nerve and the olivary eminence. The incision is designed to skirt the dorsal margin of the olive.

4. Putnam, T. J.: Progressive Confusional Syndrome Accompanying Injuries of the Cervical Portion of the Spinal Cord, Arch. Neurol. & Psychiat. **41**:298-306 (Feb.) 1939.

repeatedly. There were complete analgesia and loss of "tickling" sensation up to the first dorsal segment and hypalgesia to the sixth cervical segment. Diffuse touch, position and discriminatory senses were not disturbed. There was no motor weakness, asynergia or disturbance of skilled movement. Inequality of the pupils, with the right slightly larger than the left, was noted for two weeks after operation. Nystagmus disappeared in four days. The patient stated that her right arm felt colder than her left, but such a subjective difference was not experienced in the lower extremities. Facilities for accurate recording of cutaneous

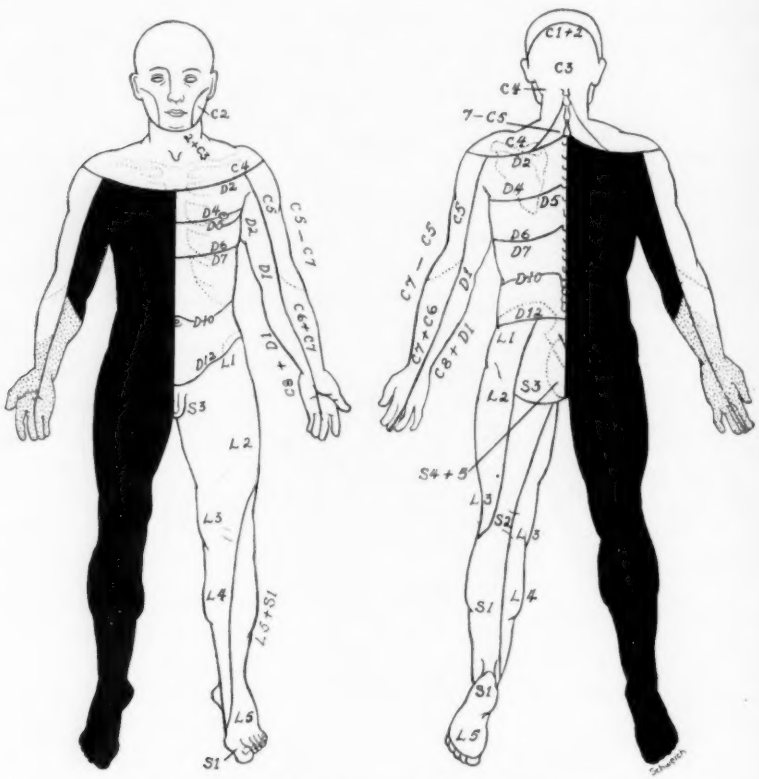

Fig. 2.—Results of postoperative sensory examination.

In this diagram areas of analgesia, thermanesthesia and loss of "tickling" sensation are solid black. Diffuse and discriminatory touch is intact. Areas of hypalgesia are stippled.

temperature were not available. On the night of operation catheterization was necessary. Thereafter there was no disturbance in bowel or bladder function.

On December 19, ten days after operation, the patient was discharged from the neurosurgical service and transferred to the orthopedic service to facilitate care of the pathologic fracture of the left hip. With the left leg supported the patient was able to be up. She was very happy and remained free of pain until her death. About Jan. 1, 1941 her general condition began to change for the

worse, and on January 3 there was roentgenographic evidence of increased hilar shadows in the left lung field, suggestive of a metastatic malignant growth. The patient died on January 7, twenty-nine days after operation.

Autopsy.—A postmortem examination was performed three hours after death by Dr. Kenneth Carter, of the department of pathology, St. Louis City Hospital. General pathologic findings consisted of carcinoma of the breast with extensive metastases to the skin, axilla, both lungs, liver, left adrenal gland and left femur.

Examination of the Central Nervous System.—Macroscopic Study: The surface appearance of the brain was normal. There were no adhesions between the cerebellum and the left side of the medulla. The contours of the two olives were equally prominent, and no discoloration or other suggestion of the site of the lesion was evident. The cerebellum was removed, and the brain stem, including the thalamus and the basal ganglia, was separated from the hemispheres. The brain stem and spinal cord were fixed by immersion in a 15 per cent concentration of solution of formaldehyde U. S. P., and all other parts were sliced and examined grossly for metastases; none was found. The stem was later divided into two parts at the level of the superior colliculi. The rostral of these blocks was cut in a frontal plane into slices 2 mm. thick. The caudal block and the spinal cord were similarly divided into slices cut in the transverse plane. These blocks were prepared by the Swank-Davenport [5] modification of the Marchi method and cut into sections 50 microns thick.

Microscopic Study.—Lesion: In serial transverse sections passing through the inferior olivary nucleus, the line of the incision was outlined by an area of primary degeneration confined to the dorsal surface of that nucleus in the middle third of its rostrocaudal extent (fig. 3 *A*). The incision entered the left side of the medulla in the postolivary sulcus and pursued an arched course medialward in contact with the dorsal margin of the olivary capsule. At a depth of 2 mm. the track branched into divergent traces, which ended 1.5 mm. farther medially. These divergent traces surrounded an apparently intact aggregation of fibers. At its terminus the lesion was separated by 4.5 mm. from the midline and by 2.3 mm. from the lateral margin of the medial lemniscus. The track of primary degeneration was narrow dorsoventrally (1 mm.) but had a rostrocaudal length of 3 mm. Several minute pockets of primary degeneration also appeared in the cell layers of the olive (fig. 3 *A* and *B*). The continuity of these with the primary lesion was not established.

Secondary degeneration at site of lesion: Some olivocerebellar and spinocerebellar fibers traversing the lesion were degenerated, and these were followed rostrally into the left restiform body. The external margin of the capsule of the olive showed heavy degeneration, which continued to the caudal pole of that nucleus (fig. 3 *B*). In part at least these degenerating fibers appeared to represent the terminal distribution of the thalamo-olivary tract. Few, if any, entered the adjoining pyramid. A few degenerating fibers were observed to pass medially through the hilus of the inferior olive and appeared to arise from foci of degeneration in that nucleus. They did not form a circumscribed bundle which could be traced to its destination.

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5. Swank, R. L., and Davenport, H. A.: Chlorate-Osmic-Formalin Method for Staining Degenerating Myelin, Stain Technol. **10**:87-90, 1935.

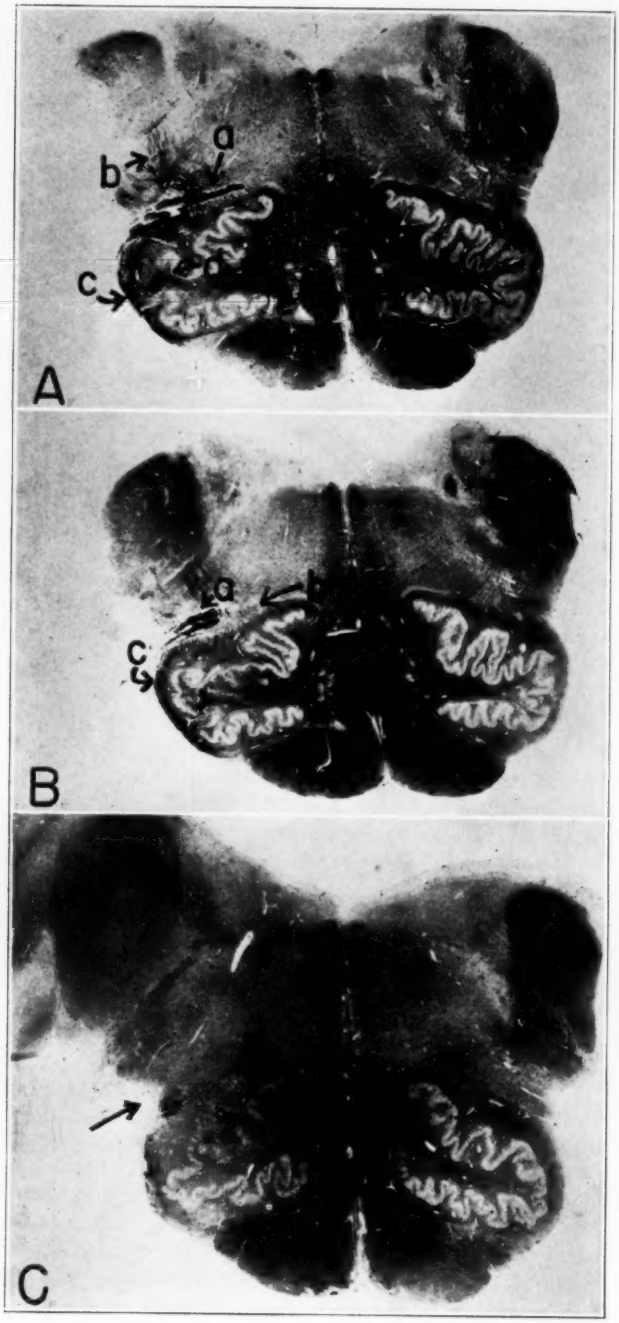

Figure 3

(See legend on opposite page)

Descending degeneration: Caudal to the line of primary degeneration that demarcated the incision, a band containing scattered degenerated fibers occupied the dorsal margin of the left olive. This bundle was wedge shaped, with its base at the postolivary sulcus. It was followed past the caudal margin of the inferior olivary nucleus, and evidently represented fibers interrupted in their cephalocaudad course by the incision. Scattered degeneration was also apparent in the right and left restiform bodies and in the tractus solitarius. The area of degeneration in the tractus solitarius was traced to a fascicle of the vagus nerve which entered the medulla caudal to the level of the incision. A few apparently degenerated fibers were seen in the left pyramid and in the right medial lemniscus. Scattered degeneration was also observed in the right postolivary area. Except for these changes the medulla was normal at and behind the level of the incision. Sections through the caudal part of the medulla and spinal cord were unsatisfactory because the rather generalized distribution of osmic acid precipitate made it impossible to distinguish between degeneration and artefact.

Ascending degeneration: The sections of the brain stem rostral to the lesion showed a compact bundle of ascending degeneration which followed the course of the spinothalamic tract, as described by Walker[1b] and, more recently, by Rasmussen.[6] Although several blocks through the rostral levels of the brain stem showed precipitation of osmic acid in the denser fiber areas, this was the only bundle that showed consistent blackening from block to block. At the level of the entry zone of the eighth nerve it was situated on the surface of the medulla ventral to the spinal trigeminal tract (fig. 3*C*); rostral to the decussation of the trapezoid body it lay lateral to the medial lemniscus; it then passed dorsally to the base of the brachium conjunctivum, where the ventral spinocerebellar tract departed to course around the brachium conjunctivum and enter the anterior medullary velum (fig. 4). The degenerated bundle was superficially situated in

6. Rasmussen, A. T.: The Lateral Spinothalamic Tract and Associated Fibers in Man, Anat. Rec. (supp. 2) **79**:51, 1941.

EXPLANATION OF FIGURE 3

Unretouched photographs of transverse sections of the medulla prepared by the Marchi method. × 3 diameters.

(*A*) The site of incision is indicated by the line of primary degeneration (*a*), which follows the dorsal portion of the capsule of the inferior olive. Thalamo-olivary fibers (*c*) and some olivocerebellar fibers (*b*) also were interrupted by the incision. There was a pocket of primary degeneration in the cell layers of the inferior olive (*d*).

(*B*) The caudal margin of the incision (*a*) is shallow at this point. Degenerating thalamo-olivary fibers (*c*) occupy the superficial margin of the capsule of the inferior olive. The scattered degeneration descending from the medial portion of the incision (*b*) is not apparent in the photograph.

(*C*) Section of the medulla rostral to the incision. The area of ascending degeneration (arrow) corresponds in position and extent to that noted following chordotomy at the eighth cervical level or below.

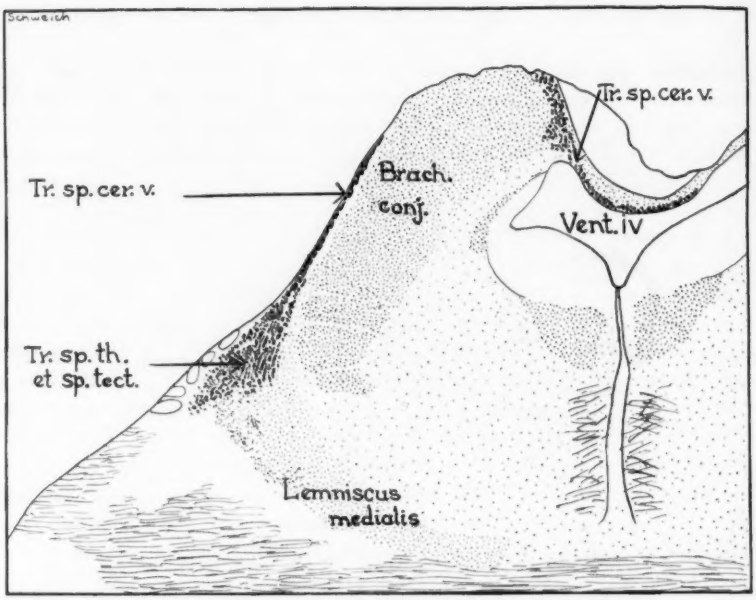

Fig. 4.—Drawing to illustrate the position and size of the bundle of ascending degeneration in the rostral part of the pons. The ventral spinocerebellar component (*Tr. sp. cer. v.*) is separating from the spinothalamic and spinotectal tracts (*Tr. sp. th. et sp. tect.*) to pass to the cerebellum. × 6.4 diameters.

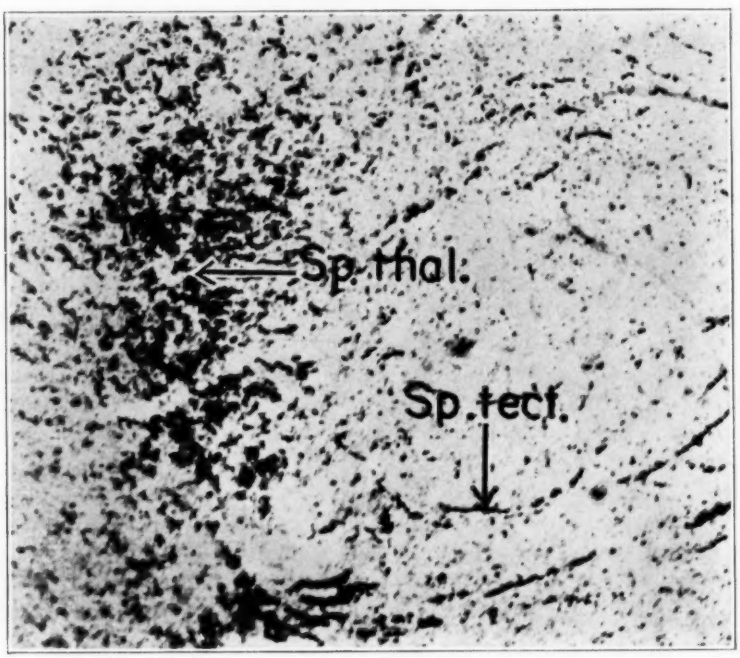

Fig. 5.—Photomicrograph to show the egress of spinotectal fibers from the spinothalamic tract to enter the inferior colliculus. *Sp. thal.* indicates the spinothalamic tract; *Sp. tect.*, spinotectal fibers. × 30 diameters.

the lateral lemniscus at the level of the decussation of the trochlear nerve; this agrees with the descriptions of Fuse,[7] Walker [1b] and Rasmussen.[6] Subsequently the bundle was found in the brachium of the inferior colliculus. At this point a group of fibers passed medially from the bundle into the inferior colliculus (fig. 5). We interpreted these to be spinotectal fibers which had accompanied the spinothalamic and ventral spinocerebellar tracts in their common course through the brain stem. Further rostrally the bundle coursed medial to the medial geniculate body (fig. 6). The thalamus was cut serially and showed degenerated fibers only in the lateral portion of the posteroventral nucleus.[1b]

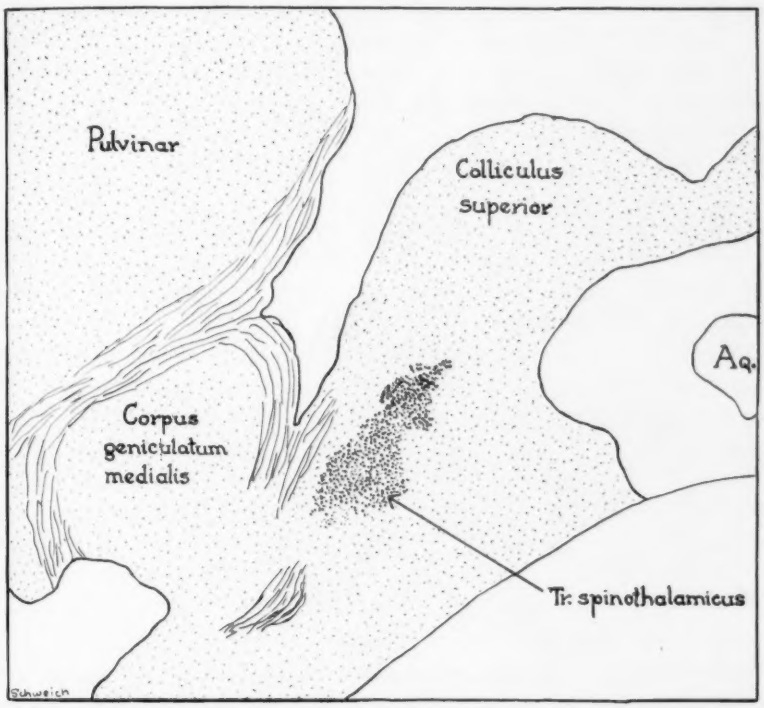

Fig. 6.—Drawing which indicates the relations of the bundle of ascending degeneration at the caudal margin of the thalamus. At this level the bundle contains principally spinothalamic fibers. × 6.4 diameters.

COMMENT

Knowledge concerning the position of fibers conveying pain, temperature and "tickle" sense from the various segments of the body has been extended to the medullary level. In 2 cases the configuration of the tract, as shown in figure 7, was established for the sequence of interrup-

7. Fuse, G., cited by Pollak, E.: Anatomie des Rückenmarks, der Medulla oblongata und der Brücke (Pons), in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 1.

tion of fibers in spinothalamic tractotomy at the level of the inferior olive. The flattened-out position of the spinothalamic tract along the dorsal margin of the inferior olive corresponds to the observations of Goldstein.[8] Rostral to the inferior olive the size, position and configuration of the area of ascending degeneration are similar to those which have been observed after section of the spinothalamic tract in the cord.[9]

As in chordotomy, interruption of the spinothalamic tract at the medullary level is complicated by interference with the spinocerebellar and spinotectal pathways. The scattered degeneration in the restiform body in the present case appeared no more abundant than the degenera-

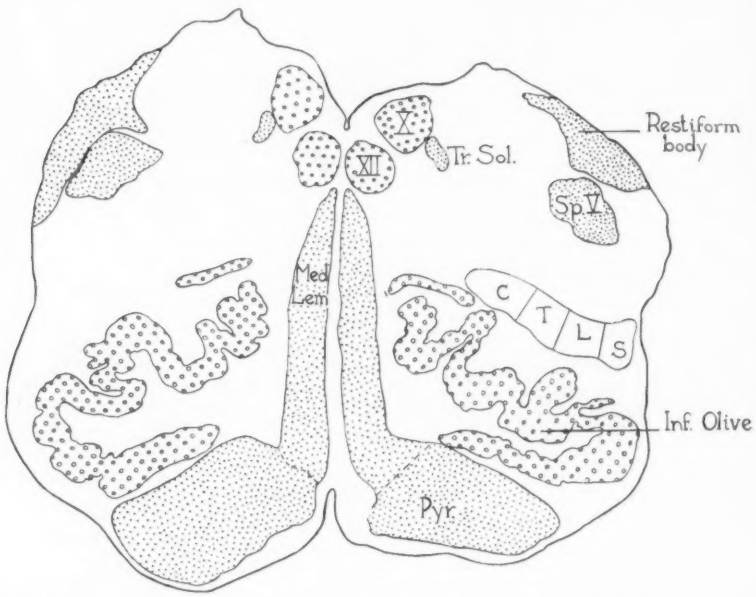

Fig. 7.—Reconstruction based on sensory examinations during two spinothalamic tractotomies at the medullary level, indicating the localization within the tract of fibers conveying sensation from cervical (*C*), thoracic (*T*), lumbar (*L*) and sacral (*S*) dermatomes.

tion illustrated in Foerster and Gagel's [1a] figure 49, which followed section of the anterolateral columns in the cord, or which we have observed in Marchi preparations in our own chordotomy cases. That elsewhere in the medulla conditions are no more favorable for avoiding spinocerebellar pathways is evident from a review of the cases reported

8. Goldstein, K.: Ueber die aufsteigende Degeneration nach Querschnittsunterbrechung des Rückenmarks (Tractus spino-cerebellaris posterior, Tractus spino-olivaris, Tractus spino-thalamicus), Neurol. Zentralbl. **29**:898-911, 1910.

9. Foerster and Gagel.[1a] Walker.[1b] Rasmussen.[6]

prior to 1900, in which the ascending degeneration following total and subtotal lesions of the spinal cord is illustrated.[10] Incision of the ventral spinocerebellar tract inevitably accompanies spinothalamic tractotomy whether the level selected is in the medulla or in the spinal cord; in the medulla damage to the direct cerebellar route via the restiform body should be minimal if the procedure previously described is followed.

Cerebellar signs have not been reported to follow chordotomy, nor did they appear in the case herein discussed, so far as the activities of the patient and objective examination could demonstrate. The pathologic fracture of the left hip, which was present before operation, prevented testing coordination in walking. Grant [11] has pointed out that an incision into the restiform body, as carried out by Sjöqvist [12] for section of the descending root of the trigeminal nerve, is followed by cerebellar disturbances. The line of incision which has been used for interruption of the spinothalamic tract in the medulla does not involve the restiform body.

We agree with Grant [11] that a correctly placed small lesion in the medulla oblongata is not necessarily hazardous to life or attended by significant or demonstrable disturbance of nerve function other than that intended by the operator. In the procedure reported in this paper, caution must be exercised in avoiding the nucleus ambiguus, which lies dorsal to the medial part of the spinothalamic tract. Further, the patient should be tested for sensory loss as the incision is deepened; this should prevent extension of the lesion into the medial lemniscus, which appears to be separated by a significant interval (2 to 3 mm.) from the portion of the spinothalamic tract containing fibers conveying pain from the cervical dermatomes. In neither of the 2 cases reported was there any damage to the medial lemniscus system.

Grant,[1c] whose experience with chordotomy has been extensive, pointed out that high cervical chordotomy is frequently not successful in relieving high pain. Of 3 cases of carcinoma of the breast with metastases to the brachial plexus, satisfactory relief of pain followed chordotomy in only 1, in which section was made at the third cervical segment. In another group of 3 cases with axillary metastases, pulmonary involvement and loss of movement of the diaphragm were present. In the latter group, Grant expressed the belief that high cervical chordotomy was contraindicated because of possible damage

10. Barker, L. F.: The Nervous System and Its Constituent Neurones, New York, D. Appleton and Company, 1899.

11. Grant, F. C.: Experiences with Intramedullary Tractotomy: IV. Surgery of the Brain Stem and Its Operative Complications, Surg., Gynec. & Obst. **72**: 747-754, 1941.

12. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve, Acta psychiat. et neurol. **17**:1-139, 1938.

to the innervation of the still functioning diaphragm. He has performed 15 rhizotomies of the posterior spinal roots from the third cervical to the second thoracic segment. Although this procedure affords relief from pain, he stated that it is not altogether satisfactory, since it necessitates a wide laminectomy of seven vertebrae and the hand and arm are entirely insensitive and useless. These considerations plus possible damage to the diaphragmatic nerve supply led us to perform section of the spinothalamic tract in the medulla in our cases.

The suboccipital approach for interruption of the secondary pain pathway from the opposite side of the body offers further opportunity for the relief of pain in selected cases of malignant growths in which the head and neck are involved as well. In such instances, spinothalamic tractotomy might be combined with section of the primary pain pathways in the fifth (by intramedullary section of the descending root [13] or by retrogasserian neurectomy according to Dandy's [14] method) and ninth nerves. All of the secondary fibers from the opposite side of the head and body might be interrupted at the midbrain by a supratentorial approach, as reported by Dogliotti,[15] and more recently suggested by Rasmussen.[6]

SUMMARY

Evidence is presented indicating the efficacy of section of the spinothalamic tract in the medulla for relief of high, intractable pain. The results of the operation in a case of carcinoma of the breast with metastases are given.

By means of the Marchi technic, the courses of the spinothalamic, spinotectal and ventral spinocerebellar tracts have been followed through the brain stem. The position of the spinothalamic tract in relation to the inferior olive has been ascertained, and a topical arrangement of fibers within the tract is described. Fibers from the lower dermatomes occupy a lateral position, while fibers from the upper ones lie medially.

13. Grant.[11] Sjöqvist.[12]

14. Dandy, W. E.: Section of the Sensory Root of the Trigeminal Nerve at the Pons, Bull. Johns Hopkins Hosp. **36**:105-106, 1925.

15. Dogliotti, A. M.: Trattamento del dolore nei tumori, Minerva med. **28**: 455-461, 1937; First Surgical Sections in Man of the Lemniscus Lateralis (Pain-Temperature Path) at the Brain Stem, for the Treatment of Diffused Rebellious Pain, Anesth. & Analg. **17**:143-145, 1938.

ESTROGEN THERAPY OF AGITATED DEPRESSIONS ASSOCIATED WITH THE MENOPAUSE

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The endocrine therapy of the agitated depressions occurring in association with the menopause has aroused interest in the past. Early experiments appeared to promise some success, but when these results could not be confirmed an attitude of pessimism developed. In recent years interest has been revived with the production of more potent extracts and the synthesis of estrogens. In the present paper the results obtained with these new products will be reviewed and 7 new cases, in which 4,4'-dihydroxy-α-β-diethylstilbene (hereafter referred to as diethylstilbestrol) was used in treatment, will be reported. An attempt has been made to include all the papers published in the more easily accessible English language journals during the seven years ending Dec. 31, 1940.

REVIEW OF LITERATURE

Casual reading of the literature suggests that no very consistent results have been obtained. Some writers have attributed their success to specific therapy; others who have been less fortunate have stressed the importance of suggestion in accounting for the favorable results. Evidence will be presented to bring these conflicting views into harmony.

The previously reported results are summarized in the accompanying table. Of the 164 women in the treated group, some relapsed after treatment was discontinued, and of these some recovered a second time under treatment. Such cases were counted only once. Of the women in the control group, 13 were treated later,[1] and of the 13, 9 recovered or improved markedly. They are included among the 164 treated patients.

Cases were selected to satisfy the following criteria: 1. The patient was treated in a psychiatric hospital. One exception to this rule was included in the table[2] because the history was sufficiently detailed to permit a diagnosis of depression. 2. The patient was treated for a minimum of ten weeks, unless she recovered sooner. 3. The diagnosis

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From the Springfield State Hospital.

1. Werner, A. A.; Kohler, L. H.; Ault, C. C., and Hoctor, E. F.: Involutional Melancholia: Probable Etiology and Treatment, Arch. Neurol. & Psychiat. **35**:1076 (May) 1936.

2. Suckle, J. E.: Treatment of Involutional Melancholia by Estrogen, J. A. M. A. **109**:203 (July 17) 1937.

Previously Reported Results of Estrogen Therapy

Dose Given in First Month *	Medication	No. of Patients	Patients Recovered or Markedly Improved	Percentage Patients Recovered or Markedly Improved	Author
Group 1: controls					
	Placebo	15	0		Werner.[1]
	Placebo	14	2		Schube, P. G.; McManamy, M. C.; Trapp, C. E., and Houser, G. F.: Arch. Neurol. & Psychiat. **38:** 505 (Sept.) 1937.
Totals for group		29	2	7	
Group 2: minimal doses					
300 to 900 R. U.	Amniotin	5	1		Bowman, K. M., and Bender, L.: Am. J. Psychiat. **11:** 867 (March) 1932.
1,500 to 4,000 I. U.	Estrone	20	14		Davidson, G. M.: Psychiatric Quart. **13:** 42, 1939.
Totals for group		25	15	60	
Group 3: moderate doses					
4,500 R. U.	Estrone	34	21		Werner.[1]
8,000 R. U.	Estrone	6	4		Little, G. A., and Cameron, D. E.: Canad. M. A. J. **37:** 144 (Aug.) 1937.
8,700 R. U.	Estrone	6	0		Schube, P. G.; McManamy, M. C.; Trapp, C. E., and Houser, G. F.: Arch. Neurol. & Psychiat. **38:** 505 (Sept.) 1937.
Totals for group		46	25	54	
Group 4: large doses					
15,000 R. U.	Estradiol benzoate	1	1		Suckle.[2]
About 15,000 I. U.	Various estrogens	23	7		Wittson, C. L.: Psychiatric Quart. **14:** 167 (Jan) 1940.
80,000 M. U.	Estrone	15	0		Notkin, J.; Dennes, B., and Huddart, V.: Psychiatric Quart. **14:** 157 (Jan.) 1940.
30,000 to 40,000 I. U.	Estrone	14	11		Ault, C. C.; Hoctor, E. F., and Werner, A. A.: J. A. M. A. **109:** 1786 (Nov. 27) 1937.
25,000 to 50,000 I. U.	Estrone or amniotin	14	6		Hutton, J. H., and Schiller, M. A.: Elgin State Hosp. Papers **3:** 183 (Jan.) 1939.
About 80,000 R. U.	Estrone and/or estradiol benzoate	1	1		Ripley, H. S.; Shorr, E., and Papanicolaou, G. N.: Am. J. Psychiat. **96:** 905 (Jan.) 1940.
80,000 to 600,000 I. U.	Estrone or estradiol benzoate	4	4		Levy, W. E.: Tri-State M. J. **10:** 2118 (Aug.) 1938.
80,000 to 600,000 I. U.	Estradiol benzoate	5	3		Dynes, J. B.: Arch. Neurol. & Psychiat. **42:** 248 (Aug.) 1939.
120,000 I. U.	Endofollicolina	1	1		Cherry, T. H.: Am. J. Surg. **37:** 302 (Aug.) 1937.
40 to 45 mg.	Estradiol benzoate	15	5		Jones, M. S.; MacGregor, T. N., and Tod, H.: Lancet **1:** 320 (Feb. 6) 1937.
Totals for group		93	39	42	
Total number of treated patients		164	79	48	

* The international unit is about one-third the rat unit.

was involutional melancholia in most instances. In cases in which this diagnosis was not made, the history was adequate to permit a diagnosis of agitated depression associated with the menopause. 4. There was no history of a psychosis earlier in life. It was hoped that by this criterion some cases of simple depression, and possibly all of them, could be excluded from the series.

Not all the cases described by the authors cited were included. A number of cases were excluded because the history was inadequate or the aforementioned criteria were not satisfied. The percentage of recovery or improvement reported here does not, therefore, always coincide with the percentage reported by the original author. Only those cases in which there was full recovery or marked improvement were counted as successes; those in which improvement was moderate or slight were counted as failures.

Inspection of the table reveals why one investigator, in considering only his own results, might easily be convinced of the efficacy of estrogenic therapy or the reverse. It is to be noted that no single hospital provided a group of patients large enough to have statistical significance.

MATERIALS AND METHODS

The success obtainable with estrone and its derivatives suggested the use of diethylstilbestrol in the treatment of psychoses associated with the menopause. The expense of the usual estrogenic preparations and the difficulty of their administration are serious drawbacks not attending the use of the new compound. This material has already been found satisfactory for the treatment of the common complications of the menopause,[3] and its successful use in a case of agitated depression was reported in a brief note by Rees.[4]

Seven patients at the Springfield State Hospital believed to be suffering from an agitated depression associated with the menopause have now been treated with diethylstilbestrol. The details of their histories and treatments are given in the following section. Six patients were treated with placebos before estrogen therapy was begun, none of whom showed any improvement. The other patient received diethylstilbestrol dissolved in milk; after recovering she declared she had received no special therapy. Four patients recovered under treatment with diethyl-

3. Collins, C. G.; Weed, J. C.; Bernstein, B. B., and Lock, F. R.: Clinical Experiences with Stilbestrol (Diethylstilbestrol), Am. J. Obst. & Gynec. **39**:117 (Jan.) 1940. Davis, M. E.: Clinical Study of Stilbestrol, ibid. **39**:938 (June) 1940. Huberman, J., and Colmer, M. J.: Effects of Di: Ethyl Stilbene (Stilbestrol) on Menopausal Symptoms, ibid. **39**:783 (May) 1940. Lewis, R. M.: Clinical Use of Stilbestrol, Synthetic Estrogen: Preliminary Report, Yale J. Biol. & Med. **12**:235 (Dec.) 1939.

4. Rees, R. P.: Stilboestrol, Brit. M. J. **1**:1056 (May 20) 1939.

stilbestrol, and 2 showed some improvement. The recovery or improvement was maintained to the time this report was written, eight months after the parole of the third recovered patient. The only toxic effect observed in any case was occasional nausea.

REPORT OF CASES

CASE 1.—B. V. was born in 1897 and had a normal birth and early development. In childhood she had frequent minor illnesses and was considered spoiled and bad tempered. The menses were irregular and painful until 1918, when a uterine suspension was done; thereafter they were normal, until the present illness. In 1925 the patient was treated for pulmonary tuberculosis for eight months at a state hospital. She never married.

In 1938 the menses ceased, and the patient complained of severe sweats. In June 1939 gradually increasing weakness, nervousness, nausea, anorexia and abdominal pain were noted. The family physician made a diagnosis of mucous colitis but was unable to relieve the symptoms. The patient became agitated and indecisive and complained of hot flashes. During the last six months of 1939 she felt hopeless and suicidal; she grew impatient and quarrelsome. She was committed to the hospital on Jan. 24, 1940, having lost 66 pounds (29.9 Kg.) since the onset of the illness.

On admission she was depressed, agitated, tense and anxious and expressed numerous complaints, especially of pain in the abdomen. Physical examination revealed a poorly nourished woman, weighing 126 pounds (57.2 Kg.). Slight peripheral arteriosclerosis was present. The results of laboratory examinations were normal.

The patient remained agitated, depressed and, as it was thought, hypochondriacal. She continued to complain of her bowels and urinary bladder, but roentgenographic studies and repeated urinalyses revealed nothing of interest. In April 1940 there was slight and temporary relief of the symptoms referable to the urinary tract under mandelic acid therapy. The weight continued to decline to a minimum of 84 pounds (38.1 Kg.) in April.

On June 5 the patient was started on a course of placebo identical in appearance with the diethylstilbestrol to be given later. No improvement occurred in two weeks of daily administration of placebos. Without the knowledge of the patient or her nurses, diethylstilbestrol was substituted for the placebo on June 19. Thereafter 1 mg. per day was given by mouth. On June 29 she ceased to be agitated or apprehensive, her appetite improved, the complaints of urinary disturbance disappeared and during the next two weeks the mood gradually became normal. July 21, when the patient's behavior had been normal for several days, the placebo was substituted for the diethylstilbestrol. No change occurred in her condition. August 5 she asked that medication be discontinued, and this was done. On September 14 she was paroled as fully recovered.

Except for slight nausea in the morning during the period of stilbestrol treatment, no toxic effects were noted. The patient's weight, which had varied irregularly between 84 and 92 pounds (38.1 and 41.7 Kg.) between April and August, rose to 98 pounds (44.5 Kg.) during the last month of hospitalization.

CASE 2.—M. R. was born in 1884 and had a normal birth and early development. After completing normal school, at the age of 18, the patient taught until a few months after the onset of the present illness, in 1933. The menses were

normal until July 1933; they then ceased until November 1933, when there was one profuse and final menstruation.

In November 1933 the patient was retired from teaching because during the preceding months she had become dictatorial, quarrelsome and overcritical in the classroom. For a few months she was depressed, then suffered screaming spells and vaguely threatened suicide. In January 1934 she was committed to a private sanatorium, where at times she was friendly and fairly cheerful and at others irritable, critical and demanding; in May 1934 she became tense and depressed. She was discharged, against advice, in May 1934 as unimproved.

In November 1934 she was committed to the Springfield State Hospital and was paroled as somewhat improved the following February. She remained at home thereafter, never entirely well and often depressed. She was returned to the Springfield State Hospital in November 1939. There was slight, temporary improvement, followed in the early months of 1940 by tension, agitation and depression. Cobra venom therapy was administered in March 1940, without effect. From June 5 to July 21 she received the same medication as patient B. V., without striking improvement. On July 21 the dose was increased to 2 mg., on July 31 to 3 mg., on August 6 to 4 mg. and on August 15 to 5 mg. per day. During the first week of August there was improvement in the appetite, but little other change until September 1, when the patient's mental state suddenly became normal. Administration of diethylstilbestrol, 5 mg. per day, was continued until September 16, when it was discontinued. From September 16 to September 21 there was moderate vaginal bleeding. The patient volunteered the statement that she had not been so well since 1932. She was paroled as recovered on October 13.

Slight nausea during the period of treatment was the only toxic effect noted.

CASE 3.—M. M. was born in 1888 and had a normal birth and early development. She had always been well until 1935, when she was told she had hypertension. In 1936 her husband had angina pectoris and suffered several severe attacks, which caused her a normal amount of worry. The menses were normal until April 1940, when they became irregular in time and duration.

In May 1940 the patient began to worry excessively about her husband's health, became depressed, wept frequently and suffered hot flashes. She failed to improve under estrogen therapy administered by her family physician or under the care of a chiropractor. After an attempt at suicide by starvation, she was committed to Springfield State Hospital on July 24.

On admission she was tense, tearful and hopeless and complained of headaches and hypertension. Physical examination revealed obesity and hypertension. Results of laboratory studies were normal.

Five days after admission the patient attempted suicide and then became so agitated that she scratched a small hole in her tongue with her finger nails. Constant restraint was necessary.

On August 7 administration of diethylstilbestrol, 1 mg. per day by mouth, was started. The medicament was dissolved in milk. On August 20 she began to take a slight interest in her environment. On August 27 she fed herself and seemed more cheerful. On August 31 the dose of diethylstilbestrol was increased to 2 mg. per day. Improvement continued until, on September 6, behavior was superficially normal. Administration of diethylstilbestrol was discontinued September 14. Vaginal bleeding began five days later and continued for two days. No toxic symptoms were observed.

During the remainder of September the patient remained cheerful, but complained occasionally that she heard voices and that the building was electrified. These ideas had not been elicited before treatment was begun because of the patient's agitation. The delusions and hallucinations gradually disappeared, and the patient was paroled October 27 as recovered.

CASE 4.—D. W. was born in 1879. Her birth was believed to be normal. She was a delicate child but was well during her adult life until the present illness. She was widowed at the age of 48 but made a good adjustment and helped to support her two children until the menopause, in 1935. At this time the patient became depressed but was able to continue doing her housework. In 1938, after the divorce of her daughter, she became more depressed, and late in 1939 she refused to eat, lost weight, acquired paranoid ideas against a neighbor, spoke for the first time in a self-accusatory fashion of her husband's death and became preoccupied, forgetful and confused. She was committed in February 1940 to a private sanatorium, where she was anxious, agitated and depressed. In May 1940, she was transferred to the Springfield State Hospital with a diagnosis of involutional melancholia, unimproved.

Physical examination revealed moderate arteriosclerosis and a blood pressure of 168 systolic and 100 diastolic. The laboratory studies gave normal results.

The patient failed to improve, and from June 5 to September 5 she was given the same medication as patient M. R. On September 5 the dose was increased to 10 mg. per day by mouth. On September 15 diethylstilbestrol was discontinued. During the period of therapy the patient gradually became less depressed and took more part in ward activities. She became able to write letters, to read and to converse more easily. Her appetite improved. However, she remained anxious and continued to express paranoid ideas occasionally.

Vaginal bleeding occurred from July 27 to July 29. No withdrawal bleeding occurred. No nausea was noted.

CASE 5.—L. McC. was born in 1895. She was a nervous, sensitive child, but made a fairly successful adjustment as salesgirl and telephone operator until her first marriage, at the age of 22. She disliked sexual intercourse and was divorced at the age of 29. One child resulted from the union. For the next twelve years she supported herself and her child by working as an operator in a beauty shop. At 41 she married again but left her husband after three months. She returned to work until her third marriage, at the age of 42. This union was also unsuccessful, because of the patient's frigidity. At 37 she had a dilatation and curettage, possibly for an incomplete abortion.

The menstrual periods were normal until the age of 42, when the present illness began. Ideas of reference developed, and two years later delusions of loss appeared. She prayed excessively and neglected her housework. In July 1940, the month before admission to the hospital, she attempted suicide three times.

On admission she was depressed, agitated, retarded and self accusatory. Physical examination revealed undernutrition and gonorrhea; the latter condition was treated successfully with sulfanilamide.

The patient failed to improve under treatment with amphetamine (benzedrine) sulfate, 10 mg. per day for two weeks. On Sept. 25, 1940 she was started on a course of placebo identical in appearance with the diethylstilbestrol to be given later. No improvement occurred in ten days of daily placebo administration. Without the knowledge of the patient or her nurses, diethylstilbestrol was substituted for the placebo on October 5. Thereafter 1 mg. per day was given by

mouth until November 7, when the dose was increased to 2 mg. per day. On December 4 the dose was increased to 5 mg. and on Jan. 3, 1941 to 10 mg. per day. On January 19 treatment was discontinued. No substantial improvement occurred during the course of treatment or up to the time this report was written, five months later.

CASE 6.—B. G. A. was born in 1897 and had a normal birth, but did not walk or talk until 3 years of age. She repeated the fourth grade four times, and all other grades were repeated at least once. At the age of 18 or 19 she had reached the sixth grade. She stopped school and thereafter worked successfully as a waitress for many years. The menstrual periods began at the age of 18 and were normal until 1933.

In August 1933 the patient became depressed and agitated. Two periods occurred in September, none in October and only a scanty flow in November and December. The patient feared she was pregnant, complained of lumps in her abdomen and hips and attempted suicide. She was admitted to the Springfield State Hospital on Dec. 24, 1933. She failed to improve until May 1934, when she was given, by mouth, a proprietary ovarian preparation, the potency of which is unknown. She began to improve at once, and on May 12, 1934 she had what she considered a normal menstrual period. This restored her spirits to normal. On May 23, 1934 she scored a mental age of 8 years 4 months on the Stanford-Binet test, with a base line of 5 years. On May 23 she was paroled and six months later was discharged.

She remained well at home until August 1940, when the depression recurred, and with it the fear of pregnancy. The patient had married a few months before. She was dissatisfied with the duration of the August and October periods, complained of pain in the hips, back and legs, slept poorly and ate little. She was readmitted to the hospital Dec. 3, 1940.

Here she failed to improve. She was agitated, depressed and convinced of her pregnancy. On December 12 she was started on a course of placebo identical in appearance with the diethylstilbestrol to be given later. One placebo was given per day by mouth until Jan. 1, 1941, without any improvement. Without the knowledge of the patient or her nurses, diethylstilbestrol was then substituted for the placebo and its administration continued until February 2. During January the appetite improved from fair to good. From February 2 to February 23 the patient received 2 mg. of diethylstilbestrol per day by mouth. During this period there was considerable increase in normal behavior. The patient became industrious and able to help with the ward work, but remained somewhat depressed, apprehensive and anxious. From February 23 to March 27 she received 3 mg. of diethylstilbestrol per day dissolved in milk. During this time she gradually recovered from her depression, but continued to believe in a half-hearted way that she was pregnant because she had had no menstrual period. Attempts to explain the menopause to her failed. Vaginal bleeding occurred from March 27 to March 31, but the patient insisted some pregnant women had vaginal bleeding. From April 7 to April 11 she received 5 mg. of diethylstilbestrol per day dissolved in milk, in an unsuccessful attempt to produce more bleeding. From April 17 to April 27 a further course of 5 mg. in milk per day was given. No further diethylstilbestrol was administered, but the patient continued to receive milk daily. On June 1, 1941 profuse vaginal bleeding occurred and convinced the patient she was not pregnant. She was then able to accept the explanation of the menopause. She remained well and was paroled June 11, 1941.

CASE 7.—D. F. was born in 1891 and had a normal birth and early development; she completed the eighth grade without difficulty. Thereafter she worked in a silk mill until the present illness. In 1911 she was operated on for gallstones. Except for this her health was good. She never married. Menstrual periods began at the age of 11 and continued to 1940, when they became irregular. During 1940 there were hot flashes, headaches and pains in the eyes. In January 1940 she became depressed, agitated and worried. She ate and slept little, feared she would be discharged and believed people were criticizing her; on November 9 she attempted suicide and was admitted to the Springfield State Hospital nine days later.

She failed to improve, and on Dec. 9, 1940 was started on a course of placebo identical in appearance with the diethylstilbestrol to be given later. She received 1 placebo tablet daily by mouth until Jan. 1, 1941, when, without the knowledge of the patient or her nurses, diethylstilbestrol was substituted for the placebo. She received 1 mg. per day by mouth until January 25. From this date to February 23 she received 2 mg. per day; from February 23 to March 27, 3 mg. per day, and from March 27 to May 8, 5 mg. per day. The agitation disappeared during the first month of therapy, and the patient became able to work in the ward. She slowly became less depressed, but continued to be very quiet and easily moved to tears. Vaginal bleeding occurred from May 13 to May 16. The degree of improvement was moderate.

COMMENT

Application of the chi square test to the figures of the table indicates a significant difference between the incidence of recovery or improvement among the 164 treated patients and that among the controls, but no significant difference between groups 2 and 4. The addition of the cases of the 7 patients treated at the Springfield State Hospital, with 4 counted as recovered, does not change the incidence of recovery or marked improvement.

For patients between the ages of 40 and 70 receiving ordinary psychiatric care in hospitals in the United States, Pollack [5] reported an incidence of recovery of 14.1 to 16.4 per hundred patients of the same age and with a similar psychosis (involutional melancholia). If Pollack's observation was based on as few as 100 cases, the difference between his incidence of recovery and that noted in the table is statistically significant. However, the figures are not entirely comparable because Pollack included no cases of patients who were only markedly improved. Similarly, his incidence of improvement is not comparable because it is based on consideration of patients showing any improvement whatever.

The success of estrogen therapy in so many cases of depression associated with the menopause is only partly satisfying. Recovery or marked improvement in only about 48 per cent of a reasonably large series of adequately treated patients leaves something to be desired, and

5. Pollack, H. M.: Outcome of Mental Diseases in United States, Ment. Hyg. **9**:783 (Oct.) 1925.

this imperfection of the results should not be overlooked simply because the incidence of recovery or improvement in the treated group is considerably higher than that in the control group.

A number of explanations for the imperfect results present themselves. Examination of the histories reported in the literature reveals that the patients were not homogeneous with respect to age, duration of psychosis, duration of hospitalization or, in detail, treatment. These factors alone might account for the failure of the response-dose curve to follow the sigmoid pattern to be expected in bioassays. However, there is probably present another, and more serious, inhomogeneity with respect to the disease. The distinction between agitated depressions associated with the menopause and other agitated depressions must be made, at present, on the basis of the history. But the history cannot distinguish between depressions due to the menopause and those following it by coincidence. It should be noted, also, that agitated depressions cannot always be distinguished with certainty from some other psychoses. Such distinctions should be made for the proper evaluation of estrogen therapy.

In view of the successes which can be obtained, however, it appears justifiable to treat all patients with doubtful conditions, with the expectation of recovery or marked improvement in about one-half. Diethylstilbestrol apparently is as efficacious as other estrogens, and certainly is more convenient than any previously used.

SUMMARY

1. Estrogen therapy cannot be considered specific for involutional melancholia in the female in the present state of ability to diagnose this disease.

2. However, it is probable that if all patients suffering from agitated depressions associated with the menopause are treated with estrogen preparations, the incidence of recovery or marked improvement will be higher than if none is treated.

3. It is probable, also, that treatment will shorten the course of the disease in those patients who respond favorably.

4. Diethylstilbestrol has been sufficiently effective in the trials reported here to warrant further use in cases of involutional melancholia.

The diethylstilbestrol used in this study was furnished by Dr. D. C. Hines, Eli Lilly & Co. Laboratories, Indianapolis.

Case Reports

"CROCODILE TEARS" TREATED BY INJECTION INTO THE SPHENOPALATINE GANGLION

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FREDERIC H. LEAVITT, M.D., PHILADELPHIA

REPORT OF CASE

History.—J. R., a white man aged 23, an American, three hours after a fishing trip noticed paralysis of the right side of his face. He could neither smile nor chew effectively. There were moderate drooling and salivation. Two days later the right side of his face became "screwed up," and he could not straighten his face. There was difficulty in eating, talking and chewing. About two years later he noticed that whenever he ate anything tears would roll spontaneously from his right eye. He could not control this, although he was told that it was just a matter of "will power." The lacrimation continued for three years, and medication was of no avail. Facial motor power had returned almost completely.

Reactions to Small Quantities of Pure, Impure and Irritative Materials Swabbed on the Inner Surface of the Cheek and Tongue *

Material	Epiphora	Blurring of Vision by Tears	Twitching of the Eyelids	Salivation
Salt	0	0	0	+
Sugar	0	—	0	+
Pepper	±	+	+	++
Cinnamon	0	—	—	+
Orange	0	±	+	+
Mustard	++	++	+	+++

* In this table, 0 indicates no reaction; ±, an equivocal reaction; +, a positive reaction; ++, an accentuated reaction; +++, a marked reaction, and — a negative reaction.

Examination.—Objectively, the patient showed good recovery of the facial musculature, although the right side of the face was slightly "ironed out." There was no ectropion. Eating of all foods caused prominent epiphora. Before lacrimation the patient experienced twitching of the right eyelid. It was noted that excessive stimulation of salivation predisposed to epiphora.

The results of stimulation of the tongue and the inner surface of the cheek with various substances are shown in the accompanying table.

Therapy.—Cocainization of the posterior naris on the side of involvement resulted in cessation of epiphora for the first time in three years. Relief lasted one hour. On the following day 0.5 cc. of sterile 95 per cent alcohol was injected into the sphenopalatine ganglion by way of the posterior palatine foramen; thereafter the patient no longer had epiphora on eating. A check on the results of operation at the end of three months revealed complete success. After four and one-half months epiphora returned.

COMMENT

The rationale for therapy arose directly from suggestions of Spiller,[1] who attributed the phenomenon of crocodile tearing to the regeneration of nerve fibers which are so misdirected that they have failed to reach the muscles which they formerly supplied. Ford [2] clearly outlined the possible pathway which these fibers assumed. The remarkable amount of muscular recovery may confuse the issue, but the necessity for interrupting the regenerating fibers by cocainization is a clue to complete therapy.

CONCLUSIONS

Effective therapy for the syndrome of crocodile tears is suggested.

The preliminary test of cocainization of the posterior naris is a clue to effective treatment.

Injection of absolute alcohol into the sphenopalatine ganglion by way of the posterior palatine foramen is recommended.

A return of symptoms may warrant reinjection of alcohol into the sphenopalatine ganglion.

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1. Spiller, W. G.: Contracture Occurring in Partial Recovery from Paralysis of the Facial Nerve and Other Nerves, Arch. Neurol. & Psychiat. **1**:564 (May) 1919.

2. Ford, F. A.: Paroxysmal Lacrimation During Eating as a Sequel of Facial Palsy, Arch. Neurol. & Psychiat. **30**:1279 (Dec.) 1933.

THE DANLOS-EHLERS SYNDROME

Report of a Case with Transient Paralysis of the Vocal Cord

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The Danlos-Ehlers syndrome is also called cutis hyperelastica and dermatorrhexis. Persons with this disorder constitute an undetermined percentage of professional contortionists and exhibitionists; they are spoken of as "india rubber men."

Ehlers [1] was the first to describe a case, and Danlos [2] established the syndrome. The condition is considered very infrequent. Prior to December 1939 only about 60 cases could be culled from the literature.[3] There are four primary signs: (1) hyperelasticity of the skin, (2) hypermotility of the joints, (3) a tendency to form abnormal and deficient scar, and (4) small tumors of the skin. Coe and Silvers [4] recently reviewed the literature and included as minor symptoms chilblains and acrocyanosis. The cause of the condition is unknown. It is classified in the group of congenital dystrophic anomalies.[3] Biopsy of the skin reveals an increase in the elastic elements.[5] Three families have been described in which the syndrome was apparently inherited as an incomplete dominant.[6] For a further consideration of the condition the reader is referred to the article of Coe and Silvers.[4]

REPORT OF CASE

J. M., aged 24 and unemployed, a patient in the urologic service of the Albany Hospital, was convalescing from a vesical diverticulectomy, which had been performed on Oct. 2, 1940. On the day following his operation the patient had a chill, his temperature rising to 104 F.; treatment with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) was instituted; the temperature returned to normal in three days, and administration of the drug was discontinued. During his stay in the hospital the patient's voice was considered harsh and high pitched, although it did not attract any unusual attention. On October 21 he awoke unable to

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From the Department of Neurology and Psychiatry of the Albany Hospital and the Albany Medical College.

1. Ehlers, E.: Cutis laxa, Dermat. Ztschr. **8**:173, 1901.

2. Danlos, M.: Un cas de cutis laxa, Bull. Soc. franç. de dermat. et syph. **19**:70, 1908.

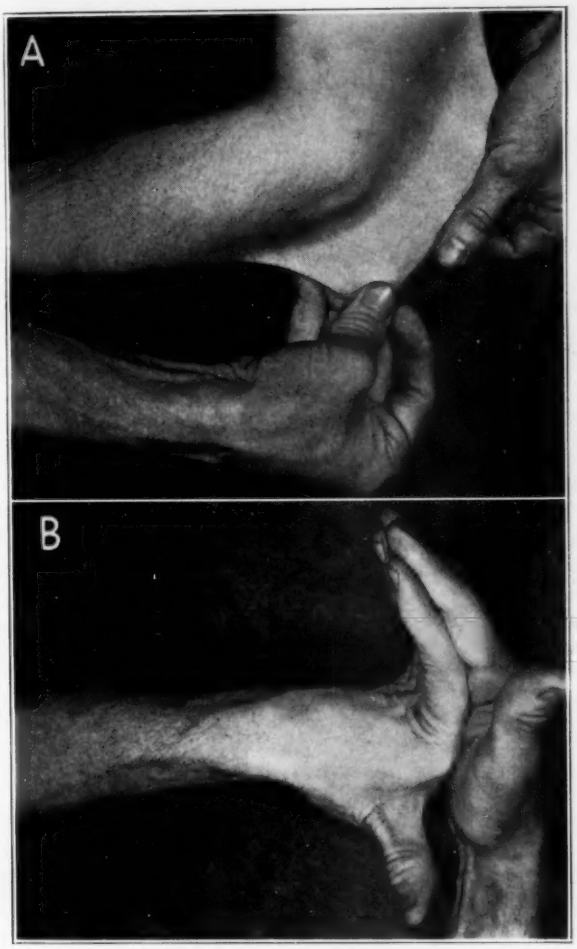
3. Skeer, J., and Kaplan, A.: The Ehlers-Danlos Syndrome, Arch. Dermat. & Syph. **42**:450 (Sept.) 1940.

4. Coe, M., and Silvers, S.: The Ehlers-Danlos Syndrome, Am. J. Dis. Child. **59**:129 (Jan.) 1940.

5. Skeer and Kaplan.[3] Coe and Silvers.[4]

6. Murray, J. E., and Tyars, M. E.: A Case of Ehlers-Danlos Disease, Brit. M. J. **1**:974 (June 15) 1940. Coe and Silvers.[4]

speak above a whisper. The laryngologist reported that there was almost complete paralysis of the left vocal cord. The difficulty in speaking gradually cleared in about five days, and thereafter no laryngeal abnormality could be detected. Roentgen examination of the neck and of the arch of the aorta gave no evidence of any pathologic process which might involve the left recurrent laryngeal nerve.



A, elasticity of the skin; *B*, hyperextensibility of the fingers.

The history and physical features were reviewed at this time. The patient had always been double jointed and had a very loose skin, "like rubber." The right shoulder had been dislocated anteriorly and replaced by the patient on several occasions. He stated that he could dislocate this shoulder and replace it with only moderate discomfort. The mother was interviewed, and examination of 2 siblings and an aunt revealed no stigmas related to the Danlos-Ehlers syndrome. There was no family history of the condition. The mother stated that

the patient's voice had always been high and scratchy and that on three or four occasions during the last ten or twelve years there had been marked impairment of speech for several days. She thought that his speaking voice was normal for him on November 1.

Examination revealed a well nourished man with marked hypermotility of all joints. The fingers could be hyperextended, the wrists hyperflexed and the feet and toes excessively plantar flexed. The skin was hyperelastic. Thus, over the chest the skin could be drawn out about 1½ inches (3.5 cm.), and it "snapped" back when released. At the elbow the skin could be stretched about 3 inches (7.5 cm.). There were several scars, measuring 2 cm., on the shins. These were healed, and the skin covering them was of the cigaret paper type. These scars were also very loose and elastic. There was a pea-sized nodule in the right cheek. A few bright silvery scars were present on the face. There were slight tremor of the outstretched hand and moderate clumsiness in writing and in doing skilled acts. The blood pressure was 140 systolic and 70 diastolic. Examination of the heart, lungs, abdomen, inguinal canals, genitalia and rectum revealed nothing abnormal. The urine was normal. The blood sugar measured 80 mg. per hundred cubic centimeters, the calcium 9.9 mg., the phosphate 3.9 mg. and phosphatase 2.1 Bodansky units. The Wassermann reaction of the blood was negative. Pathologic report revealed a bladder calculus, measuring approximately 2.5 cm. in diameter, and "diverticulum of the bladder, composed of fat and chronically inflamed vascular fibromuscular tissue, the latter covered by transitional and squamous epithelium."

COMMENT

The cause of the transient paralysis of the vocal cord in this case is not known. Nor can it be stated that its occurrence was anything but a coincidence of the Danlos-Ehlers syndrome. The infrequency of the condition and the imperfect knowledge of the nature of its minor symptoms are taken to justify the report of the case. The Danlos-Ehlers syndrome has not been described previously in conjunction with a neurologic disorder.

SUMMARY

In the case here described the diagnosis of Danlos-Ehlers syndrome can be made. There were hyperelasticity of the skin, hypermotility of the joints and a tendency to form abnormal and deficient scar. Multiple small tumors of the skin, however, were not found. During the course of hospitalization for bladder diverticulectomy, transient paralysis of the left vocal cord developed. A review of the history disclosed that on previous occasions similar short-lived episodes of difficulty in speaking had occurred. The cause of the paralysis of the vocal cord is not known; the relation between it and the Danlos-Ehlers syndrome is discussed.

News and Comment

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Psychiatry and Psychopathology

AN EVALUATION OF MANIC-DEPRESSIVE PSYCHOSES IN THE LIGHT OF FOLLOW-UP STUDIES. PAUL HOCH and H. L. RACHLIN, Am. J. Psychiat. **97**:831 (Jan.) 1941.

Hoch and Rachlin point out the variations in the incidence of the diagnosis of manic-depressive psychosis. These variations not only are regional but vary in the same region from year to year. It is concluded that the variation is in diagnostic methods and not in the incidence of the illness.

The authors substantiate this by follow-up observations and special case studies of their own, pointing out that in a large number of cases what was originally diagnosed as manic-depressive psychosis is ultmately reclassified as schizophrenia. The converse of this situation is relatively uncommon. The cases of manic-depressive psychosis in which the diagnosis was later that of schizophrenia could be divided into two groups: (1) those in which the differential diagnosis was at first impossible and (2) those in which there were mixed features.

Hoch and Rachlin conclude that the following factors point to a diagnosis of schizophrenia: incongruous statements, auditory hallucinations, paranoid delusions, projection mechanisms and ideas of reference and dissociation between motor responses and the affective component. They recommend a periodic reconsideration of the diagnosis of manic-depressive psychosis. FORSTER, Boston.

A DYNAMIC APPROACH TO THE STUDY OF REPLACEMENT THERAPY IN CASES OF CASTRATION. GEORGE E. DANIELS and EDWARD S. TAUBER, Am. J. Psychiat. **97**:905 (Jan.) 1941.

Daniels and Tauber report the cases of 3 patients (1 woman and 2 men) who were treated with appropriate endocrine preparations and given psychoanalytic therapy after surgical castration. The importance of the personality prior to castration is emphasized, as the nature and the degree of severity of psychiatric symptoms depend in large part on this factor. The necessity of careful post-operative personality studies and prolonged observation is stressed. For the woman psychotherapy alone was efficacious, while in the men regular administration of testosterone propionate resulted in increased sexual activity, evidence of which was apparent in the interpretation of their dreams. FORSTER, Boston.

THE EFFECTS OF INFANT FEEDING-FRUSTRATION UPON ADULT HOARDING IN THE ALBINO RAT. J. MCV. HUNT, J. Abnorm. & Social Psychol. **36**:338 (July) 1941.

For a considerable time psychologists, psychiatrists, psychoanalysts and some anthropologists have attributed great importance to the experiences of infancy and childhood in determining the personal characteristics of adult life. This study was conducted to obtain controlled evidence concerning the claims of psychoanalysis that experiences during infancy can affect adult behavior.

It would be highly desirable from a scientific standpoint to rear human beings under controlled circumstances. Since such a condition is out of the question, for social and humanitarian reasons, one is left with the alternative of working with lower animals.

Feeding was chosen because it is the simplest factor to control in animal work. While food storing in rats is a long cry from stinginess and collecting in human beings, it is nicely measurable and can be produced at will with a relatively slight amount of food deprivation at any time.

The feeding frustration to which the experimental animal groups were subjected consisted of ten-minute group feedings of wet mash at irregular intervals varying from nine to thirty-six hours for fifteen days. To minimize inanition, any animal failing to gain or falling in weight distinctly below its litter mates of the same sex was given extra individual feedings. Wet mash was available continuously in the cages of the controls.

Approximately five months after the end of the period of infantile feeding frustration the animals were segregated in individual cages of the hoarding apparatus. There they lived with food pellets continuously available for nine days to get them accustomed to the cages and to segregated life.

Both the experimental and the control animals were then supplied an unlimited quantity of food over a five month period. Then the experimental and the control groups—now adult rats—were subjected to a relative food famine. The object was to observe their reaction to food deprivation occurring during their maturity. After this period of food frustration in adult life they were supplied with an unlimited quantity of food pellets. Special apparatus permitted the experimenters to count the number of pellets which were hoarded by each animal.

The effect of infantile frustration on adult behavior was demonstrated by the fact that the experimental animals—those which had been frustrated in feeding at the earlier age of 24 days—hoarded more than two and a half times as many pellets as their litter mate controls, who had suffered no deprivation during their infancy.

The importance of the age at which the infantile frustration occurred is shown by the fact that another group of experimental animals in which the frustration during infancy was delayed for eight days did not resort to excessive hoarding after frustration in later life.

WISE, Howard, R. I.

A CASE OF POLLAKIURIA NERVOSA. CARL VAN DER HEIDE, Psychoanalyt. Quart. **10**:267, 1941.

The author reports the case of a girl of 23 who had suffered from pollakiuria since the age of 16. This symptom had been preceded by a period of hysterical vomiting, which began after she had a fellatio fantasy at the age of 8 years. Her character and behavior indicated that most of her life had been spent in an almost conscious struggle against being a woman.

The pollakiuria began when she found herself displaced by another girl in her older brother's affections. This reminded her of a similar displacement by a little girl who was placed in the family when the patient was 5. This traumatic experience resulted in an oral regression which aroused strong passive, dependent wishes. She was unable to tolerate the strength of these passive dependent wishes because they demanded an acceptance of feminine castration and a wish to be impregnated. She therefore began to deny her lack of a penis and to form active castrative tendencies and a phallic relation to her mother. Her vomiting was an expression of her guilt because she had a desire to incorporate orally her father's penis. The pollakiuria was: (1) a defense against her forbidden feminine wishes, as a result of which she had to eliminate actively instead of admitting her passive, receptive, feminine desires and her desire to be impregnated; (2) the expression of her desire to be a man and so a manifestation of her homosexual feelings, which came readily into play whenever she did not succeed in accomplishing her feminine desires; (3) an expression of anger, jealosy and hostility; (4) a means of obtaining infantile sexual pleasures.

Whereas the vomiting expressed libidinal wishes toward the father, the pollakiuria expressed her feeling toward her brothers. Both the vomiting and the

pollakiuria being eliminative tendencies, they expressed her feelings of guilt about her desires to receive; that is, they stated that she would not accept anything from a person whom she wished to rob.

PEARSON, Philadelphia.

MURDER IN THE EARLY STAGES OF SCHIZOPHRENIA. KARL WILMANNS, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:583 (Nov.) 1940.

Murder was committed by 18 young men who were in the early stages of schizophrenia. Although they had shown changes in personality for a long time, twelve and nine years, respectively, in 2 cases, they had never been institutionalized or become frankly psychotic. These young men had, for longer or shorter periods, a definite compulsion to kill. The author believes that the murders might have been prevented if psychiatric studies had been made. The changes in personality in 9 cases began between 14 and 15, in 5 cases between 16 and 18 and in 2 cases at 20 and 21 years of age. The murder was committed by 1 patient at 16, by 12 between 17 and 21, by 2 between 23 and 24 and by 1 at 26 years of age. In only 8 of the 18 cases was the psychosis recognized by experts soon after the murder; 7 murderers either died in prison or were transferred to hospitals for mental disease many years after imprisonment.

In many of the cases the murderers admitted they yielded to an irresistible impulse to kill. They could give no other explanation. At times they gave evidently spurious reasons for the act. In some instances they reported that they were forced to murder because of an external force, such as God or the devil. Occasionally the patients killed during morbid periods of religious ecstasy, with delusions of grandeur with a messianic coloring. Some indicated that the murder was committed to relieve intolerable inner tension and anxiety. Frequently they struck at any one about them—innocent passersby often being the victims. They often attempted suicide afterward. They usually made no effort to cover up the crime. They even notified the police of their crimes and gave themselves up. The author notes the similarity of these homicidal impulses to those encountered in patients with chronic encephalitis.

The author mentions a few famous assassins who he thinks were schizophrenic. He discusses in detail the cases of Passamante, who made an attempt on Umberto I in 1878; Guiteau, who killed Garfield in 1881, and 3 others and states that these persons were schizophrenic. The fact that persons with this condition apparently react to real situations in the early stages of their disease frequently masks their mental condition. The author notes that further observation of the course of life of some of these assassins has proved the schizophrenic nature of their mental disorder. It is not surprising that occasionally the mental content of schizophrenic patients concerns itself with political issues and resentfulness toward authority. Considering the frequent nomadism of persons with early schizophrenia, their occasional contact with anarchists, nihilists and other avowed enemies of organized government is not unexpected.

Such a murderer occasionally shows theatrical responses to his act, indicating that he is shocked by the deed and denies responsibility for the crime. While such behavior may occasionally be simulated, it is not inconsistent with the splitting of the personality so often seen in schizophrenia. More often a striking inadequacy of affect is observed. Five cases are mentioned in which the schizophrenic murderer commented on this perversion of feeling experience. The diagnosis of schizophrenia is often not made in such cases. Many schizophrenic murderers have been executed. Occasionally such a criminal is considered to have a prison psychosis which developed after incarceration. Careful anamnestic information often reveals changes in personality and character which began in early life. Further observation of the prisoner often clarifies the diagnosis, for the condition sometimes develops into typical advanced schizophrenia. The author cites 3 cases in which his suspicion that a murder was committed during the early stage of schizophrenia was corroborated by further observation of the prisoner. The large

percentage of cases of schizophrenia among murderers sentenced to lifelong imprisonment has been noted by a few investigators. Wilmanns does not believe that the mental changes are a result of prolonged incarceration. He warns against sending these patients out of hospitals, even during a remission. The homicidal tendency may recur.

SAVITSKY, New York.

MENTAL CHANGES ASSOCIATED WITH AVITAMINOSIS. A. MERZBACH, Harefuah **20**:22 (April 15) 1941.

Merzbach discusses the question of the occurrence of mental changes in cases of avitaminosis. He observed such changes in persons who had been in concentration camps. The onset of the illness in the 6 patients observed by Merzbach was insidious and usually appeared gradually over a period of a few days to two weeks. The mental picture was characterized by suspiciousness, irritability, trend reactions and querulousness. All 6 patients were between the ages of 35 and 50. The premorbid personality of all the patients was wholesome, and in none was there a family history of nervous or mental disease. The paranoid state of all the patients cleared up in two to five weeks. All received a high vitamin diet, as well as intravenous and intramuscular injections of vitamins, especially vitamin C. Three of the 6 had associated polyneuritis, which persisted somewhat longer than the mental changes. Nansen, the explorer, noted changes in behavior, such as querulousness and inability to adjust to ship routine, in sailors before the somatic signs of scurvy were observed.

SAVITSKY, New York.

Meninges and Blood Vessels

RECOVERY FROM MENINGOCOCCEMIA AND MENINGOCOCCIC ENDOCARDITIS FOLLOWING ANAPHYLACTIC SHOCK. G. BAEHR, J. Mt. Sinai Hosp. **7**:294 (Jan.-Feb.) 1941.

Baehr suggests that the universal employment of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) has served to obscure the equally dramatic crisis which signalizes spontaneous recovery in lobar pneumonia. He reports an instance which illustrates that an insignificant physical or chemical agent is sometimes capable of setting off an immunologic trigger mechanism which suddenly controls a previously overwhelming infection. After an illness of ten weeks from what appeared to be a fatal meningococcic infection, and at a time when death appeared imminent, anaphylactic shock followed by a chill and a temperature of 106.4 F. resulted in immediate and complete sterilization of the infection. Although spontaneous recovery from meningococcemia and meningococcic endocarditis is not rare, such an outcome could not have been expected in this instance. Hyperpyrexia may have played a part, as gram-negative cocci are unusually thermolabile. However, the temperature had repeatedly been as high as 105.8 F. without any influence. During the ten weeks of illness the immunologic forces had been unable to overcome the infection. The sudden and almost fatal anaphylactic shock from a drop and a half of serum, and perhaps the severe rigor and pyrexia which followed, had a rapid and profound influence on the balance between the infection and the forces of recovery. Ten days after the incident the patient, a girl of 13, was able to walk out of the hospital.

J. A. M. A.

MENINGITIS DUE TO SALMONELLA SUIPESTIFER. G. M. LYON and T. G. FOLSOM, West Virginia M. J. **37**:249 (June) 1941.

Lyon and Folsom report a case of meningitis due to an unusual small motile gram-negative rod treated with sulfanilamide. Two weeks before admission the patient, a boy 2½ years of age, became suddenly ill with fever, vomiting, malaise and diarrhea. From the parents it was learned that there had been a considerable amount of raw pork in their kitchen for two or three weeks preceding the apparent

onset of his illness. There is much reason to believe that the meningitis and the bacilluria were caused by one of the Salmonella group, probably Salmonella suipestifer (the bacillus of hog cholera) rather than Salmonella schottmülleri (paratyphoid B bacillus). Either S. suipestifer infections in man occur infrequently or they are not recognized. The young seem to be more frequently affected, and while in them the infections are believed to be mild, the most severe form is also encountered in the very young. With all the Salmonella-contaminated raw pork sold and taken into homes there have been relatively few illnesses traceable to S. suipestifer. This can best be explained on the basis of (1) the low pathogenicity of the organisms for man and (2) the failure to suspect the real causal agent. More careful bacteriologic study of the gram-negative bacilli encountered clinically would probably show a larger incidence of these infections than is generally recognized. Just what role sulfanilamide played in the management and recovery of the authors' patient is not clear. It is possible that he may have recovered spontaneously. However, it is the authors' impression that the drug was directly responsible for the recovery. They also believe that relatively high levels of the drug in the blood and the cerebrospinal fluid are required, as their patient did better clinically on high levels (from 18 to 24 mg. per hundred cubic centimeters) than on low levels (from 12 to 18 mg.). He also did better on combined oral and intrathecal administration than on oral therapy alone. At no time was there any significant evidence of toxicity other than a grayish discoloration of the skin. The authors know of no similar instance in which meningitis and bacilluria caused by a motile gram-negative bacillus were treated with sulfanilamide. Material was taken directly from the puncture needle for culture in nutrient broth. After from forty-eight to seventy-two hours a gram-negative bacillus possessing motility was observed. The bacilli were not agglutinated by serums which agglutinated the typhoid bacillus (Eberthella typhi), the Flexner dysentery bacillus (Eberthella paradysenteriae), the bacillus of paratyphoid A (Salmonella paratyphi) or the bacillus of paratyphoid B (S. schottmülleri Seiffert). In spite of the fact that the small gram-negative bacillus did not regularly satisfy all the cultural and fermentation characteristics of S. suipestifer, it seemed, on purely bacteriologic grounds alone, that the organism belonged more nearly to the Salmonella group than to any other. The finding of this motile gram-negative bacillus in cerebrospinal fluid and in the urine is of particular interest. Broth cultures from the blood gave no certain evidence of bacillemia, although they were not taken until relatively late in the clinical course and after chemotherapy was instituted. J. A. M. A.

HEAD INJURIES AND MENINGITIS. E. A. LINELL and W. L. ROBINSON, J. Neurol. & Psychiat. **4**:23 (Jan.) 1941.

Linell and Robinson report 7 cases of pneumococcic meningitis following fracture of the base of the skull. In the first 4 cases the meningitis developed rapidly —in case 1 it followed a simple fracture of the nasal bones and in case 2 a basal fracture of the skull opening into the various sinuses, and in cases 3 and 4 the infection spread along the line of fracture from a focus in the middle ear. In cases 5, 6 and 7 the meningitis occurred five, fourteen and two and a half years, respectively, after rather trivial injuries, which, however, provided pathways for the subsequent infection. MALAMUD, Ann Arbor, Mich.

SIMULTANEOUS APPEARANCE OF A BACTERIAL MENINGITIS AND ENCEPHALOMENINGITIS OR ENCEPHALOMYELOMENINGITIS. H. G. HUBER, Monatschr. f. Kinderh. **82**:283 (April 22) 1940.

Huber reports the clinical histories of 11 children aged 2 to 11 years who presented disturbances that must be regarded as manifestations of acute infectious encephalitis of unknown origin. Some of the children presented aspects of so-called idiopathic aseptic meningitis; in others the meningitic symptoms were subordinated

to encephalitic symptoms, and 1 child manifested signs of encephalomyelomeningitis. Simultaneously with these disorders in the central nervous system, serous meningitis was observed with increased frequency in adults between the ages of 18 and 35. In all the adults the disease took a favorable course, but 2 of the 11 children died. This indicates that although the acute infectious encephalomeningitis usually pursues a benign course, it does not always end as favorably as is generally believed. The observations further indicate that the so-called idiopathic aseptic meningitis may be associated with acute encephalitis and that some conditions regarded as acute aseptic meningitis *sui generis* probably should be interpreted as manifestations of acute infectious encephalitis.

J. A. M. A.

OBSERVATIONS ON EPIDEMIC MENINGITIS DURING 1940 EPIDEMICS IN HUNGARY. F. VON NÁDOSY, München. med. Wchnschr. **87**:1350 (Dec. 6) 1940.

According to von Nádosy, cerebrospinal meningitis assumed epidemic proportions in Hungary in 1939 and 1940. During the height of the epidemic, between February and June 1940, 57 female patients with epidemic cerebrospinal meningitis were treated at the author's hospital. The ages of these patients varied from 10 to 68 years. Fifty-two of the patients received chemotherapy, chiefly in the form of sulfapyridine (2-[paraminobenzenesulfonamido]-pyridine), either alone or in combination with serum. Among these 52 the death rate was 7.6 per cent, whereas the total death rate (among the 57) was 12.3 per cent. This mortality rate is favorable when it is considered that the hospitalized patients usually are more seriously ill and the mortality rate for all Hungary was 18.5 per cent. However, even a death rate of 18.5 per cent is comparatively low when it is considered that it used to fluctuate between 20 and 80 per cent. The author thinks that the reduction in the mortality is probably the result of the introduction of the chemotherapy. He doubts that "epidemic" meningitis is always caused by the meningococcus of Weichselbaum because the number of cases of meningitis caused by other organisms was considerable during the year under consideration. It is possible that these organisms (pneumococci, streptococci, staphylococci, tubercle bacilli and influenza bacilli) are causal agents only secondary to meningococci. On the other hand, it is possible that at times of epidemics as yet unknown factors produce a "predisposition" to meningitis. The author thinks that treatment with meningococcus serum was only a supporting measure, because he found that serum therapy alone had unfavorable results whereas exclusive chemotherapy produced favorable results. Sulfapyridine was given as a rule from three to four times daily in doses of 1 Gm. This medication was continued for four or five days, the total dose amounting to 15 Gm. Myodegeneration or valvular lesions indicate an unfavorable prognosis, because among the patients with these disorders there were the most fatalities. Three patients remained deaf, and in 1 case acute encephalitis caused sudden death. Of 5 patients with bloody spinal fluid, 1 died of hemocephalus internus. Myocardial changes, generally demonstrable only in the electrocardiogram, were present in almost half of the cases, but they were mild and transitory.

J. A. M. A.

SPONTANEOUS SUBARACHNOID HEMORRHAGE. H. C. A. LASSEN and T. VANGGAARD, Ugesk. f. læger **103**:427 (April 3) 1941.

Lassen and Vanggaard's discussion is based on 43 cases in which treatment was carried out during the period from 1932 to 1939. They state that spontaneous subarachnoid hemorrhage is rare in the first decade of life and after 60; half of their patients were under 40, and the average age was 40. In 42 cases there was headache, usually apoplectiform and violent, in the initial stage; pain in the neck occurred in 15, vomiting in 37, dizziness in 14, partial insensibility in 28 and complete loss of consciousness in 17. Complete loss of consciousness was frequently apoplectiform, usually of short duration. During hospitalization stiffness of the

neck was established in 40 cases, spasms in 5, a unilateral or bilateral Babinski sign in 22, absence of abdominal reflexes in 12, slight focal symptoms in 16 and massive focal symptoms in 3. In 27 out of 32 cases the temperature was normal in the initial stage. In 13 of 32 cases there were pathologic changes, most often stasis in the blood vessels of the retina; in 6 of the 13 cases grave hypertension was present. In all cases the spinal fluid was sanguinolent or xanthochromatic, with many polymorphonuclear leukocytes at the start of the disorder. Later mononuclear pleocytosis predominated. There was moderate rise of temperature after the initial stage, lasting from one to two weeks. The sensibility generally cleared up in a day or two, but in some cases unconsciousness continued until death. Removal of spinal fluid was often of symptomatic-therapeutic value, and no symptoms were seen which pointed to renewed hemorrhage resulting from reduction of the blood pressure through this procedure. The cause of the hemorrhage was established in only 1 instance—that of hemorrhagic pachymeningitis. In the 31 patients discharged the headache disappeared in from three to five weeks and stiffness of the neck in four or five weeks. Subsequent examination of 27 of the 31 patients after from one-half to seven and a half years (half of them after from three to seven and a half years) showed that 20 were fully able to work, 6 partly able and 1 wholly unable. Headache, nervousness or impaired memory persisted in 24. The likelihood of renewed hemorrhage is slight if there have been no signs of renewed bleeding during the first three months after the primary attack. Unfavorable prognosis is indicated by (1) complete loss of consciousness, (2) moderately grave or grave hypertension, (3) strongly increased pressure of the spinal fluid, (4) a positive Babinski sign, (5) spasms after the initial stage and (6) gradually increasing pulse and rise of temperature. The prognosis seems more unfavorable if there is a history of previous manifest subarachnoid hemorrhage or acute cerebral attacks with a similar picture. No plausible etiologic factor was found in 16; there were pathologic changes of doubtful significance in 9 and hypertension in 13 (marked in the 10); 1 patient had severe migraine, 1 a positive Wassermann reaction of the blood and spinal fluid without clinical signs of syphilis, 1 thrombopenia, 1 hemorrhagic pachymeningitis and 1 possibly an aneurysm of the basilar artery (clinical diagnosis). J. A. M. A.

Diseases of the Brain

SUBDURAL HEMATOMA. G. H. LAUDIG, E. J. BROWDER and R. A. WATSON, Ann. Surg. **113**:170 (Feb.) 1941.

Laudig and his colleagues studied 143 cases of subdural hematoma encountered between July 1934 and July 1939. The cases represent all patients in whom the lesion was verified either by operation or at necropsy. The data indicate that most subdural hemorrhages arise from a laceration of a cortical vessel resulting from trauma to the head. Frequently there is a concomitant traumatic lesion of the brain, and its effects cannot be delineated from those produced by the blood clot in the subdural space. A few severely injured patients will recover after the removal of the subdural hematoma, and generally the recovery can be attributed to the prompt removal of the blood clot. The clinical course of some patients who survive the acute phase of a cerebral insult accompanied by a subdural hematoma suggests that an increase in the size of the subdural collection may occur. Repeated encephalograms, at varying intervals, of patients with a subdural collection have demonstrated a progressive shift of the ventricular system away from the lesion. This shift seems to result from an increase in the volume of the collection of subdural fluid. Whenever the diagnosis of subdural hematoma is doubtful, air studies may clarify the issue. Surgical removal of a subdural collection is the only therapy. If feasible, operation should be deferred until the acute effects of the injury to the intracranial structures have moderated. The 143 instances of subdural hematoma were encountered among 10,265 cases of cerebral

injuries. The position of a subdural hematoma did not necessarily signify the region from which the bleeding occurred. Many necropsy specimens disclosed a laceration of the temporal and/or the orbital surface of the frontal lobe associated with a sizable hematoma in the parasagittal position; yet there was no injury to the crossing veins in this region, nor could attachment of the blood clot to the underlying pia-arachnoid be shown. Thirty-two patients were not operated on. They were all severely injured and died shortly after admission to the hospital. Their lesions were verified at necropsy. A subdural hematoma was suspected in many instances, but the general physical state of the patient was such that operation was inadvisable. Sixty-six of the 111 patients operated on recovered. They have been followed by the outpatient department, and their sequelae (headache, dizziness, convulsions and the like) have occurred in about the same proportion as that encountered in any group of patients who have sustained moderate to severe trauma to the brain. Three patients were committed to psychiatric care and on the average recovered in one year and were discharged.

J. A. M. A.

SUPPURATION OF THE PETROUS PYRAMID. ROBERT L. MOOREHEAD, Arch. Otolaryng. **32**:845 (Nov.) 1940.

A great deal has been written about petrositis, but few cases are encountered. In 50 per cent of them the signs vary a great deal. The infection of the pyramid occurs at the time of the infection of the middle ear, but in the majority of cases involvement of the pyramid is overlooked at that time and becomes evident only later because there may be no symptoms in the early period. The pain behind the eye is really due to a nerve outside the pyramid. Frontal pain occurs with many other conditions, as does pain in the distribution of the fifth nerve. However, pain in some part of the head is present in almost all cases of involvement of the pyramid. Paralysis due to the sixth nerve also occurs late. On the other hand, paralysis of the seventh nerve occurs with relative frequency, as the course of the nerve is within the bone itself. In many instances the paralysis clears up temporarily. Thus the history of facial weakness should be regarded as significant. The symptoms of petrositis present at the time of involvement of the mastoid also clear up temporarily in some cases, only to reappear. In other cases there is no advance warning until meningeal signs appear, as in this case: Mastoidectomy on the right side was done on a child, followed by roentgen therapy, for continued discharge from the ear. One month later the child was readmitted on account of headache and pain behind the right eye, with diplopia and vomiting. There were stiffness of the neck, a Kernig sign and 6,600 cells in the spinal fluid. A roentgenogram showed infiltration and decalcification of the pyramid. The dura was then exposed in the middle and posterior fossae, and the pontile cistern drained. Pus was found internal to the labyrinth in the middle fossa, and an opening into the bone could be demonstrated.

Chronic suppurative lesions of the pyramid may occur with no discharge from the ear. Infection in the pyramid may be dormant or unrecognized for months, or even years. The history of an aural infection occurring many months before the symptoms of petrositis, with apparently good recovery, should not be passed over. This is illustrated by the following case: A child had earache, vomiting and signs of meningeal involvement, with 750 cells in the spinal fluid, during the course of scarlet fever. Nonhemolytic streptococci were found. Large doses of sulfanilamide were given, and a simple mastoidectomy was performed. The dura and lateral sinus appeared normal. Diplopia and facial paralysis were present before operation; they gradually cleared up, the wound healed and the middle ear became dry. Five months later the child was admitted with headache, earache and vomiting. There were no local signs of inflammation about the ear drum or the mastoid scar. Lumbar puncture showed that the fluid was under pressure, with a cell content of 1,800 per cubic millimeter and gram-positive cocci. A

roentgenogram suggested erosion of the upper margin of the pyramid. Large doses of sulfanilamide were given, and fifteen days after readmission the patient was again operated on. The solid angle was removed down to the labyrinth, but no fistula was found. The pontile cistern was drained, and about 50 cc. of spinal fluid was removed. On elevation of the dura free pus was encountered internal to the labyrinth, and necrosis was found on the anterior surface of the pyramid. The child made an uneventful recovery. The infection of the pyramid was no doubt present at the time of the first operation but remained dormant for five months, with no discharge from the ear.

These 2 cases illustrate the fact that sulfanilamide and roentgen therapy controlled, but did not cure, the disease. When the infection is in the perilabyrinthine cells there may be either slight or severe labyrinthine symptoms without an actual infection of the labyrinth, as noted in a case in which mastoidectomy on the left side in a child of 8 years was preceded by temporal and occipital headache with vertigo and vomiting but with no fever. When readmitted to the hospital two months later he had nystagmus, vomiting and a staggering gait. The mastoid wound was well healed, and there was a small amount of pus in the canal. He had frontal headache, external to the left eye; the spinal fluid contained 7 cells per cubic millimeter and was not under pressure. Roentgenograms showed erosion of the whole superior surface of the pyramid, from the superior semicircular canal to the tip. At the second operation, four months after the first, the solid angle was removed down to the labyrinth and no fistula found. On elevation of the dura internal to the labyrinth, pus was encountered and the necrotic area in the bone of the pyramid was located and drained with rubber dam, followed by recovery. Of the foregoing 3 cases with subdural abscess, signs of meningeal irritation were present in 2 and absent in 1. All the patients recovered. A positive roentgenogram does not always demand an operation, nor does a negative finding exclude it. Law stated: "It is not possible to make a diagnosis of suppuration of the petrous pyramid from the information gained from the roentgenogram alone." The operation must be performed to suit the individual patient, depending on the part of the pyramid involved. In many cases, however, one cannot determine the exact location beforehand. Many patients recover spontaneously after simple mastoidectomy, at which time one should be alert for the presence of any infected tracts leading to the pyramid.

HUNTER, Philadelphia.

THROMBOSIS OF THE LATERAL SINUS AND ABSCESS OF THE TEMPORAL LOBE DUE TO BACILLUS PROTEUS. ROBERT M. DEARMIN and J. LAWRENCE SIMS, Arch. Otolaryng. **32**:1098 (Dec.) 1940.

Infection of the mastoid with Bacillus proteus causes extreme morbidity with extensive destruction of the dura. The site is usually a chronically discharging ear. Perisinus abscess, lateral sinus thrombosis and extension to the meninges and brain are frequent. Dearmin and Sims report a case with recovery.

A man aged 23 was admitted to the hospital Aug. 10, 1939 because of headache, sepsis, mental disturbance and coma. He had had bilateral purulent otitis media from the age of 6. Forty-five days after admission he became acutely ill, with symptoms of swelling about the left ear and occasional delirium. The old mastoidectomy wound began to discharge. After a month he was sent home, where he remained for one month, until the return of his symptoms. On the second admission to the hospital the patient was moribund, emaciated and stuporous, with a purulent, foul discharge from the left ear and the old mastoidectomy incision. He had bilateral papilledema, nystagmus, a positive Kernig sign and facial weakness. Study of the spinal fluid revealed a pressure of 30 mm. of mercury and 648 cells per cubic millimeter; the reaction to the Tobey-Ayer test was positive on the left, and a culture was sterile. Operation on the left mastoid revealed the presence of much foul pus, necrosis of the sinus plate and a clot filling the sinus. The dura around the sinus was granulating. The middle fossa was exposed. The dura

was normal. Search revealed an abscess of the temporal lobe 3 cm. beneath the surface, which contained 30 cc. of foul-smelling pus. Except for nausea and headache the patient made an uneventful recovery. His mental condition cleared up, and he was discharged two months after admission. Culture of material from the wound and from the abscess of the temporal lobe showed B. proteus. Culture of the spinal fluid was negative. Sulfanilamide used in the original attack was followed by regression but not by cure, which was accomplished after appropriate, extensive surgical treatment.

HUNTER, Philadelphia.

OPHTHALMOPLEGIC MIGRAINE. R. K. DAILY, Texas State J. Med. **36**:802 (April) 1941.

Ophthalmoplegic migraine, according to Daily, indicates a clinical syndrome characterized by attacks of severe headache and paralysis of the ocular muscles, with ptosis as a frequent symptom. A severe headache localized to one side develops in the course of the attack. It starts, as a rule, at the temple and spreads to the occipital and frontal regions. The headache is of the constant, dull, harrowing type, like that associated with migraine and tumors of the brain. It is accompanied by nausea and vomiting but not by scintillating scotoma or any of the visual sensations common to migraine. Nausea accompanies the headache but may precede or follow it. After from one day to a week of headache, paralysis of the oculomotor muscles sets in on the side of the pain. As the paralysis develops the headache and nausea abate, but there are cases in which this order is reversed. The duration of pain and paralysis and its extent and intensity are subject to wide variations in individual cases and in attacks. It does not seem logical that a case of persistent paralysis and a case of transitory paralysis should represent the same pathologic process. Two types may be considered: the persistent paralysis, which must remain under the suspicion of an organic lesion, and transitory paralysis, which, the author suggests, might be considered as a vasomotor functional neurosis of the posterior cerebral artery. If the process is a transitory angiospasm the result is migraine, with the various striking visual sensory phenomena. If the process is vasodilatation with edema the result is a compression of the oculomotor nerves and paralysis. The intensity of the storm is obviously greater in ophthalmoplegic migraine; the shortest attack lasts much longer than the severest attack of ordinary migraine. What factor directs the vascular disturbance into a spasm or dilatation is not known. That psychic and emotional disturbances are important exciting factors has been established. The differential diagnosis has to eliminate intracranial tumor, aneurysm of the vessels at the base of the brain, congestion of the cavernous sinus, syphilis, tabes, syringomyelia, chronic meningitis, multiple neuritis, chronic ophthalmoplegia, chronic and subacute ophthalmoplegia combined with bulbar disease and disease of the anterior horn, asthenic ophthalmoplegia, multiple sclerosis and hysteria. Treatment is that of a functional neurosis, and the prognosis is good. With a better understanding of the pathologic changes and therapy of functional neurosis, recurrent ophthalmoplegic migraine should be eliminated.

J. A. M. A.

CEREBRAL VASCULAR LESIONS AND THE TENTORIAL PRESSURE CONE. R. S. ALLISON and J. E. MORISON, J. Neurol. & Psychiat. **4**:1 (Jan.) 1941.

Allison and Morison report the case of a 10 year old child who suffered from symptoms of an abscess of the left temporal lobe which presented many diagnostic difficulties. Toward the end of the illness, the clinical picture was complicated by the sudden onset of an apoplectiform seizure followed by blindness, pupillary changes and a transient Babinski sign on the left side. Necropsy revealed an abscess in the left temporal lobe and herniation of part of the left uncus and

hippocampal gyrus through the incisura tentorii. The midline structures were displaced toward the right. The left posterior cerebral artery was stretched and displaced medially by the prolapsed gyri but was not thrombosed, and only its extreme posterior part came into contact with the free edge of the tentorium. Vascular lesions of different ages were observed in the left occipital lobe near the calcarine fissure, in the thalamus and, to a lesser degree, in the midbrain. The author is of the opinion that such remote lesions are brought about by disturbances in the vascular supply mainly through traction and kinking of, and less probably through direct pressure on, branches of the posterior cerebral artery, which result from the tentorial herniation. Such complications of the primary lesion may explain the conflicting terminal clinical signs.

MALAMUD, Ann Arbor, Mich.

Diseases of the Spinal Cord

NEUROMETABOLIC DEFICIENCY IN OLD AGE (SENILE ENCEPHALOMYELOSIS). ERWIN WEXBERG, Am. J. Psychiat. **97**:1406 (May) 1941.

Wexberg, in studies of cases of metabolic disease with involvement of the nervous system, noted a group which appeared to comprise a statistical entity. In this group the patients were between the ages of 50 and 75 years (average, 60.5), and were preponderantly females (16:10). The clinical picture consisted of myelosis and psychosis, although in some cases only one of these features was present. The psychosis was of the organic reaction type and in cases of long standing simulated simple dementia, with clouding of the sensorium. Myelosis was chiefly represented as posterolateral sclerosis, although in 1 case transverse myelitis was found and occasionally involvement of peripheral nerves could be demonstrated. Anemia was present, but varied in type.

The etiology was obscure; both dietary and endogenous factors were elicited in some of the cases. Wexberg pointed out that hypovitaminosis was not the sole causal factor, and on the basis of female preponderance he suggested an endocrine disorder as well.

FORSTER, Boston.

POSTERIOR PROTRUSION OF LUMBAR INTERVERTEBRAL DISKS. J. S. BARR and W. J. MIXTER, J. Bone & Joint Surg. **23**:444 (April) 1941.

Bar and Mixter find posterior protrusion of one of the lumbar intervertebral disks into the spinal canal to be the most common mechanical derangement of the lower part of the back in patients suffering from intractable sciatic pain. In addition, there may be associated thickening of the ligamentum flavum, chronic adhesive arachnoiditis, hypermobility of the involved vertebrae and edema of the involved nerve roots. Although the etiology of posterior protrusion of the intervertebral disks is not clear, trauma to and/or degenerative changes in the disks seem to be the usual causes. Conservative treatment should be tried in every case of suspected protrusion of the intervertebral disks unless serious nerve root pressure is obvious from sensory or motor disturbance. Bed rest and immobilization of the lumbar portion of the spine in a plaster jacket are effective means. Surgical treatment removes the ruptured disk fragment through as small a laminectomy incision as possible. Spinal fusion at the time of the laminectomy seems to give definitely better results than laminectomy alone. Of 94 patients with proved ruptured intervertebral disk whom the authors followed for at least one year after operation, 77 per cent were completely relieved of sciatic pain and in an additional 18 per cent only minor pain in the leg persisted. Two patients had proved recurrent ruptures. The relief of symptoms referable to the back was not as satisfactory as the relief of radiating pain in the leg. Of the patients in whom the spine was fused 73 per cent, and of those without fusion 52 per cent, had no symptoms referable to the back. The rest had complaints of backache or

weakness of varying severity. The end result in 20 proved cases, in which compensation was involved and the patient's medical expenses were paid by an insurance company, reveals that 9, or 45 per cent, of the patients have resumed their original occupation and consider themselves fully recovered, 6 others are at work at lighter jobs and 5 are still receiving compensation or have litigation pending and consider themselves disabled.

J. A. M. A.

NATURAL HISTORY OF HUMAN POLIOMYELITIS: I. DISTRIBUTION OF VIRUS IN NERVOUS AND NON-NERVOUS TISSUES. A. B. SABIN and R. WARD, J. Exper. Med. **73**:771 (June) 1941.

Sabin and Ward performed necropsies in 11 cases of poliomyelitis and examined various tissues to determine whether the virus was predominantly distributed in any one system. The results show that the virus is so distributed in certain regions of the nervous system and in the alimentary tract. This knowledge permits the following revaluation of the various prevailing hypotheses of the disease in human beings: 1. The absence of demonstrable virus in the olfactory bulbs and the anterior perforated substance indicates that in man the olfactory pathway need not be affected. 2. The absence of infective virus in the nasal mucosa suggests that this is not the site of multiplication and dissemination of virus. 3. The virus was not present in the salivary glands, an indication that the saliva is not a route of elimination. 4. The positive results with the tonsils and pharyngeal mucosa are probably due to the pharyngeal tissue rather than to the tonsils. 5. In the alimentary tract the virus is present not only in the contents but also in the washed walls of various parts of the tract, including the pharynx, the ileum and occasionally the colon. 6. Infection of the walls of the alimentary tract appears to be the result neither of primary localization nor of the port of entry. 7. Its distribution in the central nervous system is limited to certain areas and is not as indiscriminately disseminated as viruses (e. g., of equine encephalomyelitis), which can invade through the blood vessels or those (e. g., of rabies) which are capable of extensive centrifugal spread. 8. In the absence of evidence of any appreciable centrifugal spread to peripheral collections of nerve cells, the demonstration of virus in the abdominal sympathetic ganglia in 1 case suggests a possible route of virus progression in certain instances. The pattern of virus distribution in human poliomyelitis, according to the study, points to almost the entire alimentary tract as the primary site of attack by the virus and supports in no way the concepts involving either the olfactory pathway or the respiratory tract. The distribution also militates against the cutaneous route, although it is conceivable that occasional infection through the broken skin may be possible. There appears to be much similarity between this picture of human poliomyelitis and that of Theiler's spontaneous mouse encephalomyelitis or poliomyelitis, in which Olitsky demonstrated that the virus is carried in the intestinal tract of many normal mice, although paralysis develops in only 1 of 2,000 to 5,000 mice. The subsequent demonstration by Theiler and Gard and by Olitsky that the infectious agent is also present in the washed intestinal wall and that this is the most probable origin of the virus in the intestinal contents brings out a remarkable analogy between the two diseases.

J. A. M. A.

THE 1937-1938 EPIDEMIC OF ACUTE ANTERIOR POLIOMYELITIS IN NEW SOUTH WALES, WITH SPECIAL REFERENCE TO CHANGE IN AGE INCIDENCE, POLIOMYELITIS DURING PREGNANCY AND POLIOMYELITIS FOLLOWING TONSILLECTOMY. KAREN HELMS and W. J. WILLCOCKS, M. J. Australia **1**:467 (April 19) 1941.

Helms and Willcocks discuss certain epidemiologic features of the 1937-1938 epidemic of acute anterior poliomyelitis in New South Wales. During the first nine months of 1937 the average monthly incidence was 2 cases. Between

October 3 and October 30 5 cases occurred in the metropolitan area and 7 in rural districts. Up to Sept. 30, 1938 there was a total of 711 cases. The epidemic reached its peak earlier in the metropolitan area than in the rest of New South Wales. A study of the meteorologic elements from October 1937 to September 1938 suggests that the temperature and absolute humidity curves exhibit the closest correlation with the increase and decrease in the number of cases. The latter, commencing in the spring, attains a maximum in a midsummer month and then declines. A somewhat similar correlation was suggested in the incidence of seasonal rainfall in northern parts of New South Wales. In the metropolitan area, during the early weeks of the epidemic and while the weekly incidence was increasing, severe paralysis developed in a greater proportion of patients than during the later stages of the epidemic. In rural districts the tendency may be masked by the fact that a relatively small population is spread over a large area. The number of deaths was greater in the rural districts at the beginning and at the height of the epidemic than in the later stages. In the metropolitan area there appears to be a tendency for the age group up to 4 years to be proportionately larger and the group more than 15 years of age to be proportionately smaller at the beginning of the epidemic than in its later stages. This tendency may be masked in rural districts for the same reason that the severity of paralysis was masked. The fatality rate in New South Wales was 2.5 per cent, or 17 deaths. For the rural districts it was 4.08 per cent, or 11 deaths. The oldest patient was 63 years and the youngest 7 months of age; 64 per cent of 601 patients were males and 34 per cent females. There were only 5 patients less than 12 months of age. The percentage of patients less than 10 years of age was greater in the metropolitan area (paralytic patients 76.8 per cent) than in rural districts (paralytic patients 53.5 per cent). In the 1937-1938 epidemic of poliomyelitis in New South Wales 5 patients contracted the disease during pregnancy—1 in the fifth, 2 in the sixth, 1 in the eighth and 1 in the ninth month of gestation. A study of these cases and of 13 others reported in the literature showed only 1 in which spontaneous abortion followed closely on the infection. In 13 of the 15 cases in which pregnancy continued beyond the seventh month, the delivery and the child were normal. In the other 2 cases cesarean section was performed because of respiratory paralysis. Poliomyelitis in pregnancy uncomplicated by respiratory paralysis is not an indication for interruption of the pregnancy. In the presence of respiratory paralysis during the last weeks of pregnancy, respiration may be facilitated by the removal of the fetus. Of the 711 patients, 7 were known to have had a tonsillectomy and adenoidectomy from seven to twenty-two days prior to the onset of the illness. Bulbar and spinal paralysis developed in 3 of these 7 patients, 2 had paralysis of the palate, 1 had spinal paralysis with no evidence of bulbar involvement and 1 had the nonparalytic form of the disease. There were no deaths. A review of the literature supports the contention that operations on the throat and nose favor the development of poliomyelitis of the bulbar type. When this disease is prevalent, the risk of subsequent invasion by the virus should be well weighed before tonsillectomy or adenoidectomy is undertaken.

J. A. M. A.

FATE OF POLIOMYELITIC PATIENTS OF 1937 IN COPENHAGEN. A. MONBERG, Acta orthop. Scandinav. (nos. 3-4) **11**:184, 1940.

Monberg discusses the residual disabilities of 101 patients discharged to their homes one and a half to two years previously for further treatment of their paralytic poliomyelitis of which they had an acute attack in 1937. During 1937 there were also 25 patients who died during an acute attack of the disease and 61 who had poliomyelitis of a nonparalytic form. The surviving 101 patients with the paralytic form are divided into three groups: (1) those with mild disability, who are functionally well, as the paralysis has subsided completely or left merely some slight defects of little inconvenience to ordinary physical activity; (2) those

with moderate disability, whose functional capacity is lowered so that in order to earn their living or to do ordinary housework they must wear a supporting bandage or in whom transplantation of muscle or fixating operations on bones or joints were necessary to obtain stability of the paralyzed back or extremity, and (3) those with the severe disability, who are disabled to such an extent that they are invalids in the legal sense of the term. On reexamination 58 patients are reckoned as having mild, 24 as having moderate and 19 as having severe disabilities. Reexamination shows that the mortality for the total material was 13.4 per cent and that complete disability in the legal sense of the term was the result in 10.2 per cent, while the remaining 76.4 per cent of patients were either fully restored or able to earn their living by working after treatment with stabilizing operations or supporting bandages.

J. A. M. A.

Treatment, Neurosurgery

THERAPY IN INVOLUTIONAL MELANCHOLIA. HAROLD D. PALMER, DONALD W. HASTINGS and STEPHEN H. SHERMAN, Am. J. Psychiat. **97**:1086 (March) 1941.

Palmer, Hastings and Sherman point out the low correlation between onset of the menopause and onset of involutional melancholia. They demonstrate again the typical prepsychotic personality and the incidence of precipitating factors. They evaluate the various methods of therapy as reported in the literature and as found in their own experience. The conclusions at which they arrive are as follows: Narcosis therapy might prove on further trial to be of considerable value. The results of metrazol therapy are encouraging and seem to be almost uniform in the hands of different therapeutists. Electric shock therapy appears to be safer than metrazol therapy and may supplant it. Endocrine therapy is disappointing (failing entirely in a group of 11 females and producing improvement in but 2 of 7 males). Treatment with solution of parathyroid yielded no change in psychotic motor overactivity. Psychotherapy is of avail only in early stages and must be superficial.

FORSTER, Boston.

TREATMENT OF NEUROSYPHILIS WITH A NEW PENTAVALENT ARSENICAL, ALDARSONE. LEO SPIEGEL, WILLIAM LIEFER and HEINRICH SARASON, Am. J. Syph., Gonor. & Ven. Dis. **25**:472 (July) 1941.

Spiegel, Liefer and Sarason report the results of five years' experience with aldarsone (the formaldehyde sulfoxylate of 3-amino-4-hydroxyl-phenylarsonic acid). The drug contains 18 per cent arsenic and 7 per cent sulfur. Animal experiments demonstrated the drug's ability to penetrate into the cerebrospinal system, with but a low toxicity. Aldarsone is easily soluble in water and does not require alkalinization. The initial dose given was 0.5 Gm. intravenously. If this was well tolerated 1.0 Gm. in 10 cc. of distilled, sterile water was administered. Injections were given continuously with no rest periods, while treatment with bismuth and iodide compounds was carried on concurrently.

The cases were classified as those of asymptomatic neurosyphilis; early neurosyphilis; dementia paralytica; tabes dorsalis; tabes dorsalis with visceral crisis, atrophy of the optic nerve or Charcot joint; dementia paralytica of tabetic type; vascular neurosyphilis, meningovascular neurosyphilis and asymptomatic neurosyphilis with a curve characteristic of dementia paralytica. In all these types of neurosyphilis, improvement was noted after treatment with aldarsone. Twenty-eight patients with atrophy of the optic nerve were treated with the drug, and in no instance was increased constriction of the visual fields noted; in several an apparent expansion occurred. In all the groups treated, clinical and serologic improvement was usually noted concomitantly.

Aldarsone is well tolerated by the majority of patients. Only 9 of 133 experienced untoward reactions. One had urticaria and 1 a mild nitritoid reaction. Six patients complained of minor disturbances, such as slight malaise, faintness, fever, chills, vomiting and flushing of the face. For only 1 patient, who was diabetic, was it necessary to discontinue the drug.

BECK, Buffalo.

CONSERVATIVE TREATMENT OF SCIATIC PAIN IN LOW BACK DISABILITY. J. G. KUHNS, J. Bone & Joint Surg. **23**:435 (April) 1941.

Kuhns discusses the conservative treatment and the results in 1,000 cases of sciatic pain and disability referable to the lower part of the back encountered during the last ten years. Conservative treatment includes rest in special positions, support, medications and physical therapy but not manipulation or operative procedures. The low back pain of 519 patients had been present for two weeks or less, and that of 481 was of longer duration. In most instances the lesion causing the low back pain is presumed to be a ligamentous tear or separation of fibers at the musculotendinous junction. Pain and disability often disappear after immobilization and support, with attempted relaxation of the injured part. The best method of securing immobilization and ligamentous relaxation is to keep the patient constantly on a firm bed with the entire body horizontal except for slight flexion at the hip joint. This can be secured in the supine position by placing a pillow under the knees, or in the prone position by placing it under the abdomen. If the ligamentous injury is severe it may be necessary to apply a plaster back shell or a plaster spica for immobilization. In most instances while the patient is in bed physical therapy, daily use of heat, should be given to the posterior surface of the spine and pelvis to improve local circulation, relax muscular spasm, relieve pain and hasten the absorption of inflammatory exudate. As soon as muscular spasm and pain begin to subside and the patient can move in the bed without much discomfort, exercises to teach him muscular coordination are begun. The average period of complete recumbence was ten days. It should be continued until pain and local tenderness subside. This is not the end of treatment, as usually prolonged convalescence is required for the patient to be able to resume his usual activities. Because the time required to heal a ligamentous tear is long and an unguarded movement during convalescence may cause recurrence, a spinal support is advisable. For the author's patients an average of forty-eight days was required before the spinal symptoms and signs subsided and the patients returned to work. The extremes were one week and ten months. Some patients who return and continue at work are never wholly free of symptoms, although physical signs do not suggest a spinal lesion. The reasons for their continued symptoms may be colon chronic arthritis; a congenital anomaly, making the back potentially weak; working long hours with the back bent, or inability to learn to use the body in a more correct habitual position. Of the 1,000 patients treated conservatively for the relief of local and referred pain, the pain of 771 was relieved, that of 72 was not relieved and the result for 157 is not known. Of 449 patients with sciatic radiation of pain, 356, or 79 per cent, were relieved. The study suggests that all patients with acute traumatic and chronic postural strains of the lower part of the back can be expected to recover under conservative treatment. The length of treatment will depend on the severity of the trauma, the chronicity of the lesion and the cooperation of the patient. For those patients with structural changes in the vertebrae or their contiguous structures in whom structural restoration cannot be expected, as in cases of metastatic malignant growths, conservative therapy may prolong function and is a definite palliative measure. If normal osseous contour is established, conservative therapy is necessary for the recovery of normal function. For the group of patients with pain in the lower part of the back from pressure or irritation within or about the spinal canal, conservative treatment may be of little benefit. If a definite lesion exists, its removal is indicated. The author had no patients with pain referred to the back from other parts of the body, usually the abdominal and pelvic viscera, but says that the lesion that causes the referred pain should be treated.

J. A. M. A.

TREATMENT OF PENETRATING WOUNDS OF THE BRAIN. C. PILCHER, J. Tennessee M. A. **34**:166 (May) 1941.

Pilcher points out that most penetrating wounds of the brain in civilian and in military life are cared for by the general surgeon, who should remember that every compound fracture of the skull is potentially a penetrating wound of the brain. Treatment should not be attempted without adequate neurosurgical facilities. First aid should consist of superficial cleansing and shaving, control of hemorrhage and treatment of shock. Most important is rapid transportation to a point at which operation can be performed. During transportation the head should be moderately elevated (unless shock is present). Evacuation of the wounded by airplane, as it is now practiced by the German army, has met with considerable success. However, in open head wounds the low atmospheric pressure of high altitudes may increase cerebral herniation. In the author's experiments, immediate removal of foreign bodies in twelve hours resulted in 75 per cent recovery and their removal after twenty-four hours resulted in 75 per cent fatality. The complete removal of foreign bodies is not always feasible or wise. Great depth of penetration or lodgment in the hemisphere opposite the point of entrance renders removal difficult, and the damage caused thereby is too great to justify the procedure. The bullet itself is not often a source of pathogenic bacteria. Contamination is much more likely to arise from fragments of skin, hair, clothing, dirt and other material that has been driven in. If cleansing is complete and damaged tissue thoroughly removed, and if the wound is closed within a few hours, the danger of a retained projectile is minimized. The brain tolerates foreign bodies well. The author cites 2 cases which support the rational advice of Cushing that foreign bodies should be removed only if their removal does not increase the existing cerebral damage. The location and depth of the wound influence not only the degree of residual disability, if the patient recovers, but his chances of recovery. In addition to the high mortality resulting from laceration of large arteries or the great venous sinuses, penetration of the ventricular system (particularly if early operation is not possible) and injury of the brain stem, midbrain or hypothalmic region are of grave prognostic importance; they usually terminate fatally. These structures may be unexpectedly involved by seemingly distant wounds. For patients not seen until frank infection is present (or in the borderline period from twelve to twenty-four hours, when infection may develop) immediate open drainage offers the only hope of avoiding a fatal outcome. The bony opening should be from 3 to 4 cm. in diameter, the dura left open and a soft tube, or even small gauze packing, inserted to the bottom of the cavity. The once dreaded cerebral fungus will develop. However, the danger from it is in reality small if drainage is adequate and the cerebral infection becomes localized. For the patient seen after healing of such an infection because of convulsions, paralyses or other disabling symptoms, excision of the cicatricial mass is indicated. The author states that, for traumatic neurosurgery, carefully trained and experienced operative teams and elaborate equipment, though desirable, are not essential. However, two devices, a strong suction apparatus and a high frequency, damped wave electrosurgical unit are almost indispensable. Without them adequate débridement and control of hemorrhage are all but impossible. All macerated scalp tissue, free fragments of bone, devitalized brain tissue and accessible foreign material should be removed, but the injury already sustained should not be increased. Gentle irrigation will "float up" all but the largest foreign fragments, and careful suction will cleanse the tract and facilitate complete hemostasis. Temporary gentle packing with moist cotton may be useful. Gauze should never be used on the brain. All wounds free of infection should be closed tightly with fine silk. A drain inserted into the brain is an open invitation to infecting organisms, and it increases the danger of cerebral herniation. If loss of skin has been extensive, it may be possible to close the defect by "relaxation incisions." The exact field of usefulness and the true effectiveness of sulfanilamide and its derivatives in management of craniocerebral wounds contaminated by bacteria have not yet been finally determined. The Canadian and German armies are using them for prophylaxis and therapy. Extensive studies on the subject are in progress.

J. A. M. A.

Society Transactions

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

BERNARD J. ALPERS, M.D., *President, in the Chair*

Annual Meeting, Atlantic City, N. J., June 9, 1941

Encephalitis with Intranuclear Inclusion Bodies: A Clinicopathologic Study. DR. A. J. L. AKELAITIS and DR. L. J. ZELDIS, Rochester, N. Y.

This paper will be published in full in a future issue of the ARCHIVES.

Correlation of Vital Observations with Postmortem Study of the Cerebral Circulation. DR. LEO ALEXANDER, DR. M. KORB and DR. T. P. SOHLER, Boston.

The object of this study was to determine whether and to what extent the vascular reactions which can be observed in the living animal through the Forbes window remain recognizable in postmortem specimens of brain tissue removed after the animal has been killed at the termination of the experiment.

Our studies showed that certain of the physiologic phenomena observed were preserved to a remarkable degree in benzidine-stained specimens obtained post mortem. The most complete correlation of vital and postmortem observations is that shown by the changes produced by dehydration. The physiologic aspects of the changes in dehydration were described by Forbes and Nason (ARCH. NEUROL. & PSYCHIAT. **34**:533-547 [Sept.] 1935). The outstanding physiologic changes described by these authors consisted of dilatation of the pial arteries and a fall in spinal fluid pressure. The correlated pathologic changes are equally remarkable. Gross specimens of the brains of cats which during life had been dehydrated by a 50 per cent solution of urea injected intraperitoneally, with or without the use of salyrgan given intramuscularly, reveal a remarkable degree of shrinkage (pseudoatrophy), such as that described in man by Alexander (ARCH. NEUROL. & PSYCHIAT. **32**:933-962 [Nov.] 1934) and by Alexander and Wu (ARCH. NEUROL. & PSYCHIAT. **33**:72-122 [Jan.] 1935), as well as dilatation and increased filling of the pial vessels. Benzidine-stained preparations of the brain show remarkable dilatation and increased filling of the intracerebral vessels of all orders of magnitude throughout the gray and the white matter of the brain. This pattern of maximal vasodilatation was observed through the Forbes window during the life of the animals.

Toxic reactions produced by the use of various drugs were characterized by well marked changes in the intracerebral vascular pattern post mortem. The correlation of the intravital response of the pial vessels with the postmortem appearance of the intracerebral vascular pattern, however, was less complete than in the dehydration experiments because of the greater variability of the blood pressure response. When the blood pressure reaction is taken into account, the postmortem picture can be understood on the basis of the physiologic observations, and conclusions concerning the physiologic phenomena preceding the death of the animal can be drawn from the study of the postmortem specimens stained with benzidine. Four types of cerebral cortical pattern were distinguished: (1) normal filling, (2) arteriolar and capillary hyperemia, (3) venous and capillary hyperemia and (4) patchy or laminar anemia (blanching), with or without alternating areas of venous and capillary hyperemia, the hyperemic areas being observed with or without perivascular hemorrhages.

The fourth type of pattern was rather characteristically observed in those animals in which a remarkable decrease in blood pressure had taken place once or more times during the experiment. This decrease in blood pressure may throw light on the origin of disseminated areas of blanching, with or without stasis and perivascular hemorrhages in adjacent districts, which occur in the course of systemic diseases, as well as a disseminated complication of localized craniocerebral trauma. It suggested that such lesions when found in cases of craniocerebral trauma may not always be caused directly by the trauma but rather may be related to episodes of decrease in blood pressure secondarily associated with the trauma.

Changes in the Brain Associated with Electrically Induced Convulsions in Cats. Dr. B. J. Alpers and Dr. J. F. Hughes, Philadelphia.

This paper will be published in full, with discussion, in a future issue of the Archives.

Progressive Subcortical Encephalopathy (Binswanger's Disease). Dr. Charles Davison, New York.

Progressive subcortical encephalopathy was first described by Binswanger in 1894, when he recognized it as a form of cerebral arteriosclerosis with involvement of the white matter and sparing of the gray matter of the cerebral hemispheres.

REPORT OF A CASE

C. W., a man aged 65, awoke one morning with blurring of vision, numbness of the face, inability to talk, difficulty in swallowing and regurgitation of food on attempting to eat.

General and Neurologic Examination.—The blood pressure was 210 systolic and 120 diastolic. The arteries of the extremities were thickened and tortuous. The fundi showed normal disks, with slight distortion of the veins and sclerosis of the arteries. There was voluntary facial paralysis bilaterally. The patient could not close the eyes, wrinkle his forehead or approximate his teeth. Reflex closing of the eyes and facial movements on laughing, however, were preserved. The mouth was kept slightly open. The palate could not be elevated. The tongue could not be protruded, but no atrophy or fibrillation was present. There was impairment of all forms of sensation over the face. The pharynx was completely insensitive, but pharyngeal reflexes could be elicited. The jaw jerks were hyperactive and equal on the two sides. There was bilateral hyperreflexia, without a Babinski or other pathologic reflex. Sense modalities over the body were not impaired.

The laboratory data were negative.

Course.—The aforementioned symptoms improved somewhat, and the facial paralysis cleared up on both sides. About nine months after the original onset of the illness there appeared suddenly aphasia and inability to move the left arm. In addition to the aforementioned symptoms, examination at this time disclosed the following changes: partial sensory and motor aphasia, perseveration, anomia, increased reflexes bilaterally and positive Hoffmann, Babinski and Chaddock signs on the left. After this episode there were increased mental confusion, marked restlessness, euphoria and disorderliness in conduct.

Autopsy.—Postmortem examination revealed extensive areas of demyelination, limited to the white matter in the first orbital convolution, the premotor convolutions, the right insula, the parietal region and the left temporal convolutions. The demyelination was more marked in the center than at the periphery. The U fibers were spared in most instances. The demyelinated areas were filled with compound granular corpuscles. The small blood vessels of the white matter disclosed thickening of the intima and obliteration and narrowing of the lumen. The architecture of the cortical layers of the involved areas appeared well preserved.

Comment.—The process in this case was analogous to that described by Binswanger in subcortical encephalopathy. There was no evidence of any inflammatory reaction. The early picture of pseudobulbar palsy with involvement of the nuclei of the fifth sensory and the seventh nerves could be explained only on the basis of vasospasm of some of the vessels of the medulla oblongata.

DISCUSSION

DR. G. B. HASSIN, Chicago: Did Dr. Davison study the spinal cord, and did he see there any of the areas of demyelination which were so extensive in the brain?

DR. CHARLES DAVISON, New York: Study of the spinal cord revealed no areas of demyelination. There were no abnormalities of the cord except for atherosclerosis of some of the vessels.

Unusual Observations in a Case of Carbon Monoxide Poisoning. DR. G. EROS, New York.

The brain weighed 1,250 Gm. and its substance was hyperemic. The globus pallidus on both sides appeared normal, without the characteristic bilateral symmetric softenings.

Histologic study showed conspicuous changes in the white matter throughout the brain. The Spielmeyer stain for myelin sheaths revealed confluent patchy and diffuse demyelination of the white matter, except in a narrow subcortical zone. Fat stains showed fatty disintegration of the myelin sheaths and accumulation of fat scavenger cells in these areas. Moreover, diffuse proliferation of the fibrous glia could be observed. The glial proliferation was perivascular, and the patchy areas of demyelination showed some relation to the blood vessels of the white matter.

In the basal ganglia proliferation of microglia and macroglia cells, perivascular fat scavenger cells and a few perivascular hemorrhages were seen. The special stains for myelin sheaths, fat and glia showed a picture similar to that of the cerebral white substance. Similar but milder changes were present also in the thalamus, the mesencephalon, the pons, the medulla and the cerebellum. In the demyelinated areas of the white matter and the basal ganglia slight symptomatic inflammation was represented by perivascular accumulation of round cells.

Histologic study of the several cortical regions revealed diffuse neurocellular changes. In the nerve cells degenerative changes, swelling, vacuolation, shrinkage, marked fatty infiltration and total disintegration were seen. In many places circumscribed areas of cellular loss were present. These alterations were most conspicuous in the third and fifth cortical layers. There was marked proliferation of the microglia and macroglia cells with neuronophagia throughout the entire cortex. The lamina zonalis was thickened, owing to proliferation of the fibrous glia. The marked fatty degeneration of the nerve cells was the most conspicuous change in the cortex. The thickened molecular layer contained many gitter cells.

The vascular system of the brain showed severe alterations, due partly to arteriosclerosis and partly to gas poisoning. Acid fuchsin stain of the blood vessels showed small and large confluent, circumscribed areas in the hyperemic cortex, with no or with diminished capillary pattern. Conversely, in the vicinity of these absolute capillary proliferation could be observed, producing capillary bundles in many places. The small arteries and precapillaries of the cortex divided at a sharp angle into two to eight parallel coursing precapillaries and capillaries respectively. The newly formed rami, each of the same or similar caliber, formed characteristic brushlike bundles, similar to the bundles of blood vessels described by Cerletti in cases of pernicious malaria.

Dropping out of capillaries and capillary proliferation could be seen also in the basal ganglia, especially in the striatum.

It seems likely that this marked capillary proliferation is the consequence of the anoxemia and capillary damage caused by the poison, as anoxemia and toxic effects presented similar pictures in the cases of pernicious malaria described by

Cerletti. I may mention here that I have seen similar capillary proliferation and bundles of blood vessels in cases of pernicious anemia and other severe anemias by application of the acid fuchsin stain.

Another sign of the damage to blood vessels in this case was the marked hyalinization of some of the cortical arteries and precapillaries. These hyalinized vessels showed markedly thickened homogeneous walls, which stained deeply with fuchsin, and diminution of the lumen. A great number of hyalinized capillaries were observed also in the subcortical nuclei.

The large arteries and the arteries of medium size showed arteriosclerotic changes, including degeneration of the elastic membrane, fibrous thickening of the intima and thickening of the entire wall.

Summary.—In this case, which differs from many cases of carbon monoxide poisoning described in the literature, there was no softening of the basal ganglia. Conversely, the severe patchy and diffuse deep demyelination of the white matter and the marked vascular damage and capillary proliferation constitute an unusual feature. The severe vascular damage and the marked secondary capillary proliferation support the theory that damage to the brain produced by carbon monoxide is due to anoxemia and severe functional and anatomic vascular changes.

Pathologic Alterations at the Human Synapse. Dr. J. Minckler, Omaha.

Of 8,104 *boutons* counted in the spinal cords of 19 persons without neuropathologic conditions, 18.53 per cent appeared granular in form in block silver sections. In similar preparations from 78 persons with neuropathologic conditions, 32.79 per cent of 41,458 *boutons* appeared granular. The incidence of granular forms in the different groups of cases was as follows: 21.84 per cent of the 9 cases of arteriosclerotic myelitis or myelopathy; 29.83 per cent of the 11 cases of metabolic or malnutritive disturbances, including inanition; 31.46 per cent of the 11 cases of toxic conditions; 31.67 per cent of the 10 cases of tumor; 33.18 per cent of the 12 cases of trauma; 35.32 per cent of the 11 cases of meningitis, and 40.74 per cent of the 14 cases of an inflammatory state. The average number of *boutons* per anterior horn cell section, for example, is 5.16 in the cases of noninvolvement of the neurons and 5.92 in the cases of neuropathologic disturbance. This slight increase is attributed to early inflammatory beading in the terminal fibrils which is prominent enough to show in the total averages. This may be important when transcribed to equivalent on a whole cell, the total surface area of which may be over 50,000 square microns (posterolateral column), about 48 per cent of which is engaged in synaptic contact. In a series of selected severely damaged cords the average number of *boutons* per cell section varied somewhat with the condition of the cell in relation to which the *boutons* terminated (4.1 *boutons* per cell section in 2,329 normal-appearing cell sections, 3.35 *boutons* per cell section in 1,870 slightly damaged cell sections and 3.22 *boutons* per cell section in 333 irreversibly degenerated cell sections). The reduction in number is most striking around cells undergoing degeneration by neuronophagia. It is concluded that the nerve terminals of the human cord exhibit both morphologic and numerical changes under pathologic influence.

Neuropathologic Changes in Experimental Carbon Disulfide Poisoning in Cats. Dr. A. Ferraro, Dr. G. A. Jervis and Dr. D. J. Flicker, New York.

Five cats were used. Each animal was placed in a large box of about 750 liters capacity for a period which varied from case to case. From 6 to 7 Gm. of liquid carbon disulfide was placed in a large dish over a slightly warmed electric stove and introduced into the box. After complete evaporation the air of the box contained 8 to 10 mg. of carbon disulfide per liter. The volume of the box guaranteed a sufficient supply of oxygen.

The clinical signs shown by the cats during exposure to gas varied. Increased salivation and dyspnea were frequent. Vomiting was only occasionally observed. Restlessness and excitement were common in the first stages of intoxication. At more advanced stages apathy was observed, and in a few instances coma inter-

vened. Tremors and muscular jerks were also frequent, but convulsions were observed in only 1 instance. All these symptoms disappeared in a few hours after the animal was taken from the box. During the interval, except for a certain apathy, the most striking symptom was a fine tremor involving the head and at times the whole body. Histopathologically, the fundamental process in the brain was represented by (1) vascular and (2) neurocellular involvement.

The vascular involvement consisted of a diffuse process of thickening of the blood vessel walls, associated with a certain amount of proliferation of capillaries. Occasionally the thickening was more marked and was at the expense of the intima. Vascular changes were diffuse in the various cortical areas but involved also the caudate and lenticular nuclei. The involvement of the thalamus was less pronounced and the red nucleus seemed free from vascular damage. Conversely, the tectum of the mesencephalon and pons, the quadrigeminal bodies and, in the medulla oblongata, the area of the vestibular nuclei constituted areas of predominance of the vascular lesions. The cerebellar nuclei showed also marked vascular damage. Here and there, particularly in the dentate nucleus, the involvement of the blood vessels led to softening.

The cellular pathology was expressed in terms of diffuse degenerative changes of nerve cells all over the cortex, the subcortical structures and the cerebellum. The changes ranged from chromatolysis and acute swelling to severe degeneration of Nissl. Some of the cells, although pyknotic and shrunken, appeared vacuolated. When degeneration was most severe acellular areas resulted. A certain number of cells disclosed hydropic changes. In most of the areas where the vascular damage was more pronounced the cellular changes were more substantial. In general, the chromatolysis, with pallor of the cytoplasm and slight pyknosis, was one of the most common neurocellular changes.

The mechanism by which these morphologic changes in the neurons are brought about is likely to be found, among other factors, in the well known narcotic action of carbon disulfide, which is similar to the action of ether and chloroform. In addition to the direct effect of the gas, the involvement of the blood vessels, with its related disturbance in circulation, undoubtedly plays an important role in the pathogenesis of the lesions.

This paper was published in full in the November 1941 issue of the ARCHIVES OF PATHOLOGY, page 723.

Myatonia Congenita (Oppenheim) Accompanied by Congenital Intraspinal Tumor, Developmental Retardation and Malformation. DR. F. H. LEWEY, Philadelphia.

The pathogenesis of myatonia congenita (Oppenheim) is still highly controversial, despite the reports of 23 cases in which necropsy was performed. The authors who found pathologic changes exclusively in the muscles expressed agreement with Spiller that the disease represented "an arrest in the development of the muscles." Seven of the 15 authors who observed pathologic changes in the cells of the anterior horns and in the anterior spinal roots concluded that the disease was a fetal form of progressive spinal muscular atrophy (Hoffmann-Werdnig type) with secondary alterations in the muscles. However, 8 authors voiced serious objections to this concept. They stressed the fact that the electrical reaction of the neuromuscular system and the histopathologic changes in both the nervous system and the muscles speak in favor of developmental retardation or malformation. In the opinion of these authors the muscular alterations do not follow but parallel the disease in the nervous system. Their conclusion is confirmed by the observation that in 11 cases the pyramidal tracts, the posterior columns or the spinocerebellar tracts were only partially myelinated or were not myelinated at all at the end of the third month of life and that in 3 cases the white matter of the brain was incompletely myelinated and the cortical and cerebellar cells were involved. In 4 instances, finally, dysplasias were reported in siblings of the patient or malformations in the patient himself. The theory of developmental retardation or malformation is further strengthened by the report

of 3 new cases in which the clinical and pathologic picture of myatonia congenita was accompanied by (1) a lipoma of the cervical portion of the cord, (2) an ependymoma of the sacral portion of the cord and (3) aplasia periaxialis diffusa.

This paper was published in full in the January 1942 issue of the *American Journal of Diseases of Children,* page 76.

Ganglioneuroma of the Left Thoracic Cavity. Dr. K. Löwenberg, Ann Arbor, Mich.

Clinical examination revealed a poorly nourished girl of 8 years with asymmetric chest, the left lung being flattened. Percussion revealed marked flattening over the entire left side of the chest. Heart sounds were absent posteriorly. The right side of the chest was normal. There were no palpable masses in the abdomen. Equinovarus was present.

Roentgen examination of the chest showed a large, partly calcified tumor filling the left side of the thorax.

Operation revealed that the tumor extended deep into the intercostal spaces between the seventh, eighth, ninth and tenth ribs and was attached to the periosteum. The tumor reached up to about the level of the third rib and extended around and in front of the aorta, thus straddling it. Several intercostal nerves were seen to enter it. The mass was removed with difficulty, but the patient died suddenly.

Pathoanatomic Report.—The tumor was oval, hard and yellow. It weighed 605 Gm. and measured 16 by 10 by 6.5 cm. Histologic examination showed numerous large ganglion cells with poorly developed tigroid bodies and frequently two to five nuclei. All the cells were unipolar, with poorly developed processes. Numerous myelinated fibers were embedded in large wavy bundles of connective tissue. The tumor apparently arose from a spinal ganglion.

Comparative Data on Tissue Culture of Acoustic Neurilemmoma and Meningioma. Dr. Margaret R. Murray, New York.

The in vitro outgrowth from 2 tumors of the cerebellopontile angle which we have studied is quite distinct from the outgrowths similarly cultured of 3 leptomeningiomas and 1 hemangiomatous meningioma.

The angle tumors produced a characteristic schwannian outgrowth of the same general type as that produced by other tumors of the peripheral nerves and by normal nerves, both fetal and adult. The type cell is that which grows out from the A areas and is similar in vitro to the normal sheath cells from Remak's fibers and from the fine medullated fibers. This cell at first appears in single, filamentous form and is often multinucleate. Later it thickens, forming a ribbon or a bundle of parallel filaments, and it may finally, after a month or more of cultivation, appear as a bundle or tuft of ribbons. From the B areas (or regions of microcystic degeneration) the outgrowth consists typically of a semiameboid, highly liquefactive, sometimes phagocytic cell, which emerges early in the course of culture and forms characteristic treelike, often multinucleate growths. It is distinct from macrophages or monocytes. Sometimes it forms reticulate structures reminiscent of the B areas in sections. Numerous transitional forms exist between this cell and those of the A type.

The Schwann cells in these cultures produced small amounts of reticulin in the form of long, single fibers, running parallel with the long axis of the cell. These did not appear first as a mat of fine, crisscross fibers, and they took from two to four times as long in forming as those which appear around fibroblasts. Fibers were not usually observed in connection with other types of cells in these cultures.

In the meningioma cultures, the type cell is a broad, flat cell resembling endothelium or mesothelium, though this cell may also adopt a fusiform, or even a greatly elongated bipolar, shape. In its flat form it grows in a semimembranous sheet, which appears like a mosaic of irregular blackened cement borders when

treated with silver nitrate. These cells frequently show fibroglia or tonofibrils and have a frayed appearance when treated with the common fixatives and stains. Present also are numerous macrophage-like cells and some long filiform cells resembling desmoblasts. None of these cells produced collagen or reticulin in vitro.

DISCUSSION

DR. A. P. STOUT, New York: Dr. Murray's demonstration of the marked cultural differences between the neurilemmomatous angle tumor and the meningothelioma has convinced me that the two neoplasms are quite different. In the one case the cells are capable of forming a smooth surface and can wrap and fold themselves about blood vessels in a complex manner; in the other the cells tend to form a syncytial, open mesh cytoplasmic sheath and reenforce it by manufacturing delicate reticulin fibers.

Dr. Murray and I together have studied cultures of a variety of normal cells and the tumors which come from them. We have been impressed both by the individuality of different cell types and by their versatility. For example, the behavior and morphologic character in vitro of Schwann cells and fibroblasts are entirely different, so that one can easily distinguish them; yet both are able to form reticulin fibers. We believe that the method will help in obtaining a better understanding not only of the morphology and function of the more obscure normal cells of the body but of the nature and cellular origin of many debated tumors.

DR. I. M. TARLOV, Brooklyn: When one looks at a peripheral nerve in section, the Schwann cell and nucleus appear very large, much larger than the endoneurial fibroblast. Why is it, Dr. Murray, that in your cultures this difference in size is reversed?

DR. MARGARET R. MURRAY, New York: The Schwann cell is extremely variable in its morphologic character, and this is partly due to the physical conditions under which it finds itself. It varies in size all the way from the sheath cell of the fibers of Remak, which is known to be a fine, filamentous cell, to the sheath cell of the large motor fibers, with their heavy envelope of myelin. In the latter case the cell forms only a thin film over the bulky medullated axis-cylinder, and when its contents are absent, the Schwann cell does not remain distended but shrinks to proportions more like those of the cells covering the unmedullated fibers. We have seen this transformation actually take place during the course of wallerian degeneration in vitro, as the myelin and axis-cylinder are progressively resolved inside the Schwann cell.

The endoneurial fibroblast also is subject to its physical environment. When growing freely in the medium of a tissue culture, it tends to spread out and become fanlike or spatulate, but when compressed in a nerve fascicle it adopts more economical, fusiform proportions.

DR. I. M. TARLOV, Brooklyn: One of the objections to the contention of Nageotte and Masson that the longitudinal reticulin fibers of the nerve sheath are formed by the Schwann cells is based on the fact that fibroblasts are also present in the immediate vicinity of these fibers. Can you be sure that the reticulin fibers appearing in your cultures are not produced by fibroblasts or blood vessels?

DR. MARGARET R. MURRAY, New York: Dr. Tarlov's question is a natural one. We have been very careful to exclude from consideration all fibers which might possibly have been formed in connection with fibroblasts, macrophages or blood vessels. The reticulin fibers which we have reported on were formed exclusively in the vicinity of and bear a definite relation to cells which we regard as Schwann cells, never to cells which we regard as fibroblasts.

DR. G. LIEBERT, Elgin, Ill.: If these tumors are composed of Schwann cells, why is no myelin found in them?

DR. MARGARET R. MURRAY, New York: I cannot answer this question. I do not know how myelin is formed; I suppose it to be produced by some inter-

action between the Schwann cell and the axis-cylinder. These tumors contain a few, a very few, neurites, and it is true that these are unmyelinated. But that in itself is not a departure from normal conditions, since many axis-cylinders remain permanently unmyelinated.

Section of the Cephalic Third of the Vagus–Spinal Accessory Complex: Clinical and Histologic Results. DR. I. M. TARLOV, Brooklyn.

This paper was published in full in the January issue of the ARCHIVES, page 141.

Further Investigations on a Myelolytic Substance Present in Disseminated Sclerosis. DR. A. WEIL, Chicago, and DR. G. HEILBRUNN, Elgin, Ill.

After the study of the myelolytic action of such substances as bile salts, saponin and snake venoms on the myelin sheaths of the spinal cord of the rat (*Arch. Path.* **9**:828 [April] 1930) the attempt was made to demonstrate the presence of myelolytic substances in disease processes which are characterized pathologically by selective destruction of myelin in the central nervous system. Many authors, for example, Bruce and Dawson (*Tr. Roy. Soc. Edinburgh* **50**:517, 1916), whose work greatly stimulated this investigation, had previously assumed the presence of such substances in disseminated sclerosis. Weil, Luhan and Balser (*Tr. Am. Neurol. A.* **61**:142, 1935) demonstrated myelolytic substances in the urine in about 70 per cent of cases of disseminated sclerosis, substances which were not of the nature of ferments but which rather resembled in their effect the destructive action of bile salts on myelin sheaths. During the interval following the first publication the attempts to purify such myelolytic substances were continued. The first step had been precipitation from the alcoholic extract of concentrated urine by acetone. Next it was found that dioxane (diethylene dioxide) extracted the myelolytic substances from the acetone precipitate and from the concentrated urine. From the dioxane extract the substances could be precipitated by ether. The material thus purified was extremely hygroscopic and highly surface active. But it lost the latter property and the myelolytic effect when exposed to the air. Similar substances with a high degree of surface activity could be isolated from normal urine, but they were not myelolytic.

It appeared that the myelolytic substances eliminated in the urine of patients with disseminated sclerosis were more frequently found during exacerbations of the clinical symptoms than during remissions. This was demonstrated by a patient who had been regularly examined during the last eight years.

DISCUSSION

DR. A. FERRARO, New York: Dr. Weil has mentioned that myelolytic substances in the urine of patients with parkinsonism were found in a very high percentage of cases. It seems to me that this statement throws doubt on the specificity of this substance for the myelin sheaths inasmuch as one rarely finds demyelination in cases of chronic encephalitis.

DR. A. WEIL, Chicago: In answer to Dr. Ferraro, I might say that in the present stage of this investigation one is not able to make any statement as to whether these substances are chemically identical in the two diseases. In cases of syphilis of the central nervous system or of subacute combined degeneration of the spinal cord such substances were never found. However, they can be demonstrated in the urine in cases of hepatic disease combined with jaundice. In the literature there are many reports of severe metabolic disturbances in cases of postencephalitic parkinsonism (Rossie, Froment and Veluz and others). Furthermore, it is not known how important are other accessory factors, for example, permeability of the blood vessels, predisposition of myelin sheaths to the attack, concentration and periodicity of elimination of the myelolytic substances into the blood, etc. At present one only can point out the presence of myelolytic substances in certain types of nervous disease, but it is too early to enter into highly speculative deductions about their etiologic significance.

The Brain in Sickle Cell Anemia. Dr. F. Wertham, Dr. N. Mitchell and Dr. A. Angrist, New York.

This paper will be published, with discussion, in a future issue of the Archives.

Progressive Degenerative Encephalopathy: Report of a Case Occurring in Infancy with Antenatal Onset in Which the Condition Simulated "Swayback" of Lambs. Dr. N. W. Winkelman and Dr. M. T. Moore, Philadelphia.

The purpose of presenting a single case of a demyelinating disease is to call attention to several of its important features: (1) its onset prior to birth; (2) its similarity to "swayback" in lambs (which is also antenatal) and (3) its relation to Schilder's disease.

Our case is that of an infant, the first child of young parents, who was born after prolonged labor and required strenuous measures for resuscitation. The birth weight was 7 pounds (3.2 Kg.), but the child did poorly from the start and lived but twelve weeks. Three days after birth a spinal puncture revealed bloody fluid under 300 mm. of pressure. From birth the infant showed spastic diplegia. Later there occurred convulsive seizures, inability to swallow, vomiting and diffuse eczema.

The brain was much smaller than the intracranial cavity, in which fluffed-out, loosely adherent leptomeninges were present. The surface of the cortex appeared and felt gelatinous, and the gyri, especially of the parietal lobes, were extremely small and numerous. Coronal sections revealed diffuse, symmetric, cystic gelatinous degeneration of the greater part of the subcortex, with sparing of the subcortical ganglia. The cortex was greatly thinned. The cerebellum showed diminution in relative size of both the folia and the white substance, but no cyst formation.

Microscopically there were complete diffuse demyelination of the hemispheric white matter, with symmetric cavity formation as the result of liquefaction necrosis, and incomplete demyelination of the cerebellar white matter. The astrocytes were increased and showed progressive and regressive changes. The spaces in the spongy areas contained numerous fat-laden gitter cells. The axis-cylinders were sparse, tortuous and swollen.

The cerebral architecture was disarranged, with decreased numbers and immaturity of ganglion cells, increase in astrocytic glia and phagocytic cells containing fat. The subcortical ganglia showed severe gliosis with marked accumulation of gitter cells. Here the ganglion cells were sparse, and many were calcified.

In this case there is both a clinical and a pathologic similarity to the "swayback" of lambs. "Swayback" is manifested clinically by early onset of motor weakness, spasticity, occasional blindness and a progressive course, terminating in death. Pathologically, "swayback" shows diffuse symmetric demyelination of the cerebral white matter, with liquefaction and cavity formation. The similarity to Schilder's disease and to some of the other demyelinating diseases in human beings is apparent, as indicated by Innes and Shearer.

This case, of the reported cases of a demyelinating disease in man, represents the closest approach to "swayback" of lambs. Since the latter has been established as antenatal in origin and since there is a clinical and pathologic similarity between it and the disorder in our case, we believe that the condition in our case developed in utero. The presentation of this case may throw light on some of the conditions heretofore attributed to birth trauma.

DISCUSSION

Dr. L. S. King, Princeton, N. J.: It is worth pointing out with respect to "swayback" that a group of Australian investigators have laid especial stress on the role of copper in the diet of the ewes. It has been claimed that when affected flocks were shifted to other parts of the country where the copper content of the food was normal the condition was abolished in the lambs.

Pathologic Features of Murine and Cavian Poliomyelitis. Dr. A. Wolf, New York.

Jungblut and Sanders induced an infection of the central nervous system in cotton rats by inoculation with the brain and spinal cord of monkeys infected with poliomyelitis virus (SK strain). This was transmitted in turn to white mice and from these to guinea pigs. The murine infection was characterized by moderate anterior poliomyelitis, chiefly lumbar, and severe polioencephalitis, most marked in the frontal portion of the cerebrum, less so in the brain stem and least in the cerebellum. In the anterior horns ganglion cell necrosis was moderate or marked; diffuse polymorphonuclear or lymphocytic infiltration was mild or moderate; microglial reaction was moderate; congestion and edema were slight or mild, and perivascular round cell infiltration was slight. The lesions in the brain were of the same general character. Round cell infiltration of the leptomeninges was slight and strictly related focally to the parenchymal lesions. In the guinea pigs very severe lesions occurred in the anterior horns of the lumbar and cervical enlargements, and less often elsewhere, frequently spreading to the posterior horns. Ganglion cell necrosis was intense; the microglial reaction was moderate or marked; edema and congestion varied from mild to marked, and the diffuse polymorphonuclear and, to a less degree, the lymphocytic infiltration varied from moderate to very marked. Perivascular and leptomeningeal round cell infiltration was mild, but somewhat more pronounced than in the mouse. Cerebral cortical lesions were few and relatively small. The basal ganglia, diencephalon, cerebellum and brain stem were only rarely and mildly involved. Other organs in both the mouse and the guinea pig showed only incidental, unrelated lesions. In summary, the white mouse infected with the SK strain of poliomyelitis virus by way of the cotton rat showed moderate poliomyelitis and marked, often predominating, encephalitis. The guinea pig infected in turn with the murine strain showed poliomyelitis closely resembling the anthropoid and human type with little associated encephalitis.

Tumors of the Brain Produced with Benzpyrene. Dr. H. M. Zimmerman and Dr. H. Arnold, New Haven, Conn.

All previous efforts to produce brain tumors with benzpyrene have been unsuccessful. For this reason, it is of some interest that when 3,4-benzpyrene in pellet form, without dilution with any foreign lipoid, was implanted intracerebrally in C_3H mice, brain tumor developed in a high percentage of cases. In many respects these neoplasms resembled those produced with 20-methylcholanthrene under similar experimental conditions.

In addition to many primary intracranial sarcomas, a variety of gliomas were produced, among them ependymoblastoma, glioblastoma multiforme, oligodendroglioma, astrocytoma and several unclassified tumors. Many of these new growths had the gross and microscopic architecture of their counterparts in human beings. The more malignant tumors frequently became partially hemorrhagic and necrotic, showed a tendency to metastasize along the cerebrospinal fluid pathway and contained numerous cells in mitotic division. Subcutaneous transplantation of the tumor was shown to be a means of perpetuating each new growth for an indefinite number of generations.

Infundibuloma. Dr. J. H. Globus, New York.

The term infundibuloma is suggested for a tumor of the brain thought to be derived from embryonal remnants of the infundibular stalk. It duplicates the histologic appearance of the posterior lobe of the pituitary with an additional characteristic feature, which comprised vessels bearing a striking similarity to those of the infundibular region in the maturing brain during the early postnatal years.

The tumor is interpeduncular in location, solid in structure and very vascular. Two cases, both of children, are reported.

DISCUSSION

DR. L. S. KING, Princeton, N. J.: Shortly after I completed the work with Wislocki on the vascular supply of the hypophysis and adjacent regions, I had the opportunity of studying the cytology of the area postrema. This small region in the fourth ventricle has many points in common with the infundibulum, especially in relation to the vascular arrangement and the reaction to vital dyes. Cytologically this region resembles the posterior lobe of the hypophysis, and presumably the infundibulum as well, although no special work on the latter point is available. I can confirm the statement that the usual glia stains are not effective in impregnating the special cells of this tumor. Success was obtained only with the double impregnation method of Hortega. This is another link between the area postrema and the infundibulum. It is desirable to consider as a group these special areas of the nervous system, which include as well the preoptic recess and the paraphysis; a blastomatous change in one of them, as Dr. Globus has demonstrated, should lead one to pay more attention to the others.

DR. O. MARBURG, New York: There seems to be a rule that the structure of a brain tumor depends on the site of its development. Therefore tumors of the infundibular region are supposed to present the characteristics of this region. Credit is due Dr. Globus and his co-workers for having shown a few years ago the peculiarity of the infundibular structure, though they did not reveal the cause of this peculiarity. Much of it has been explained by Tilney's investigations on the morphology of the diencephalic floor.

Like Edinger, Tilney found that the infundibulum has an anterior, or ventral, pituitary surface and a posterior, or dorsal, saccular surface, the latter representing the saccus vasculosus. Anterior to the infundibular process, behind the chiasm, is the postchiasmatic eminence, and laterally, the lateral eminence. Between the infundibular process and the mamillary bodies is the postinfundibular eminence, the eminentia saccularis Retzius. All these eminences consist of bulgings of the third ventricle, covered with ependyma. The recess in the infundibular process is deep in lower animals, while in apes and man it is only a small groove.

As for the structure described by Globus: I have found a marginal zone consisting of an extremely fine network of delicate glia fibers, inside this zone a few layers of glia cells and inside these layers a network of coarser glia fibrils with many cells. Most remarkable are the blood vessels, which enter the process in radial fashion and are invested with a fine network of delicate glia fibers similar to that in the marginal zone. This structure is to be seen not only on the saccular surface but, though perhaps to a slightly less marked degree, on the pituitary surface, where the floor seems to be a little thicker and contain increasing amounts of nerve tissue. Incidentally, I have been studying for months the glandular structures around the third ventricle (subcommissural organ; thalamic gland). It seems to me that the infundibular process belongs to these glands.

There are cases of normal persons in whom the hypothalamus resembles the state of lower animals, with branching diverticula of the infundibular process, which thus approaches the structure of the saccus vasculosus.

Types of Softening of Central Nerve Tissue. DR. G. B. HASSIN, Chicago.

Aside from the vascular type of softening, very common in the brain and spinal cord, two other types should be considered—degenerative and traumatic. These three types possess a common histologic feature—transformation of the nerve tissue into lipoids which are enclosed within microglia fat granule bodies (gitter cells). The reactive tissue phenomena, however, differ. In the vascular type of softening the reaction is mesodermal—the softened nerve tissue is invaded by proliferated connective tissue and transformed into a connective tissue scar. The glia and microglia succumb together with the nerve parenchyma. In the degenerative type of softening the degeneration of the nerve fibers is caused by the direct action on the nerve fibers of a toxic-infectious agent, without the intermediation of such factors as thrombosis or embolism. The reaction in

degenerative softening is in the nature of microglial proliferation, without connective tissue scar formation. The glia is also involved, though occasionally it exhibits progressive changes. In the traumatic type of softening the pathologic process is similar to that which takes place in degenerative softening, again depending on the intensity and extent of the trauma. The fat granule bodies in this type of softening are also microglial, but no proliferation of connective tissue with formation of fibroblastic scar tissue takes place. A noteworthy feature common to both the degenerative and the traumatic type of softening is absence of capsule formation around even the well circumscribed, smallest foci of degeneration.

The tissue reactions occurring in all these forms of softening differ from those seen in multiple sclerosis, in which the reactive phenomena, including the scar formation, are purely glial. Were the histologic changes in multiple sclerosis due to a vascular factor, the reactive phenomena and the scar would be mesodermal, which, as has been stated, is not the case.

Vascular Malformations and Vascular Tumors Involving the Spinal Cord: A Pathologic Study of Forty-Six Cases. Dr. O. Turner and Dr. J. W. Kernohan, Rochester, Minn.

This paper was published in full in the September 1941 issue of the Archives, page 444.

DISCUSSION

Dr. A. Weil, Chicago: Did the authors, in their cases of hemangioblastoma of the spinal cord, find similar tumors in other organs, or were the lesions associated with Lindau's disease?

Dr. J. W. Kernohan, Rochester, Minn.: Craig, Wagener and I are reporting a case of Lindau-von Hippel disease in which we found a hemangioblastoma in the spinal cord. In a case in which we had an opportunity of making an examination about fourteen years ago characteristic features of Lindau-von Hippel disease, such as polycystic pancreas, were present, except that there were no retinal hemangiomas.

Our material for the most part was obtained from the neurosurgical service, and we have no information about the other organs.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

James B. Ayer, M.D., *Presiding*

Regular Meeting, Oct. 16, 1941

War Neurology. Dr. D. D. Denny-Brown, London, England, and Boston.

War creates a multitude of problems in medicine, not only in surgical organization, technic and judgment but in almost every other branch of medicine. To neuropsychiatry is entrusted the heavy responsibility for some of the most difficult decisions—the handling of the high percentage of enlistment disabilities as well as the numerous war casualties resulting from psychoneuroses, the complex judgments concerning the ability of commanders and pilots to return to duty after disability and decisions with regard to disabilities resulting from injuries of the brain, cord and peripheral nerves.

Problems related to enlistment disabilities and early breakdown during service were first described. The prominence of gastric neurosis and the minor degrees of mental deficiency in particular were discussed. The importance of educating the unit or battalion medical officers in the handling of early neurosis was stressed.

The difficulty in rehabilitating men for civilian work after breakdown in the services has required the setting up of special centers, where neuropsychiatric supervision is essential.

In land battle rapid movement requires special units, both surgical and medical, to be situated far behind the lines. A number of scattered small units appear to be more manageable than single large organizations, both in neurosurgical and in neuropsychiatric work. The speed and comfort of modern transport of casualties have made it possible to base large units in the home country. The transfer of men with spinal injuries was discussed, and preference for early suprapubic drainage with careful nursing was expressed.

The great importance of adequate field records—especially in regard to conditions of coma, stupor and restlessness—was emphasized, and a special field card with provision for simple "yes-no" answers was recommended.

The lecturer then dealt with his special experience in treatment of head injuries. Case histories were cited to show the importance of apparently trivial scalp wounds in relation to surgical complications. A careful history and the evaluation of pretraumatic personality are essential in establishing emotional and anxiety factors, which must be assessed in all cases of head injury in order to arrive at a sound judgment with regard to ability to return to duty, especially in the case of airmen. The electroencephalogram and the air encephalogram are of great assistance in assessment of injury to the brain but cannot be used alone, for the constitutional psychoneurotic factors present can be fully assessed only by means of interviews and the history. Traumatic epilepsy is already a considerable problem, and statistics parallel those from the last world war.

Civilian psychiatric casualties from bombing were stated to be much less numerous than might be expected. The prominence of hysterical fugues and the relative scarcity of hysterical paraplegias, contractions and mutism were discussed.

The delays in recovery of nerve injuries have been greatly shortened by early exploration and definition of the injury. The scarcity of causalgia was attributed to the great reduction in wound sepsis. In such cases as do occur the psychologic management is of importance. In men unaccustomed to much walking (and the infantry still marches long distances) many mild deformities of neuromuscular type, such as pes cavus from old poliomyelitis, assume prominence and can be treated effectively when recognized.

Obituaries

MENAS SARKAS GREGORY, M.D.

1872–1941

The sudden death of Dr. Menas S. Gregory took from us a man who had played a unique and important role in the development of psychiatry in New York city. Primarily he was a practicing and practical psychiatrist, and this role he played so well that he made many friends for psychiatry among the general public, the legal profession, the judiciary and legislators.

His friends knew little of Dr. Gregory's early life. He was born in Marash, Armenia, in 1872 and was graduated from Central Turkey College (an American institution) with a degree of Bachelor of Arts in 1894. He must have come to this country shortly after this, for his record shows that he was graduated from the Albany Medical College in 1898, where he had been a classmate of Thomas W. Salmon. After graduation he served on the staff of the Craig Colony for epileptic patients, at Sonyea, N. Y., but he left there soon and went to New York city, where he started in private practice.

In 1904 he was appointed director of the psychiatric division of Bellevue Hospital, and here he began his real life's work. This was an especially difficult job and one in which none of his predecessors was able to last more than a year. Dr. Gregory held this position for thirty years and by his diplomacy and tact made friends for his service and for psychiatry, especially among lawyers and in the courts. The Bellevue psychopathic division absorbed most of his interest and ambition. It was truly his life. He was constantly planning for it and scheming for its advancement with politicians and makers of city budgets. He planned so well for it over the years that the modern building which now houses the psychiatric division will always be a monument to Dr. Gregory. Before he retired in 1934, he had succeeded in getting for the division just about everything his ambition had planned for it.

For some time before 1916 Dr. Gregory taught psychiatry at Columbia University. He was professor of psychiatry at New York University from 1916 to 1934 and emeritus professor after that. In 1909 he was elected an active member of the American Neurological Association. He was likewise a fellow of the American Psychiatric Association, a Fellow of the American Medical Association and a member of the New York Psychiatric Society (president, 1930–1932), of the New York Society for Clinical Psychiatry (president, 1925–1927), the New York Neurological Society and the New York Academy of Medicine.

Gregory will be missed by his many friends. Psychiatry was his major interest, and its only rival was his golf. He died while playing golf on Nov. 2, 1941.

LOUIS CASAMAJOR, M.D.

Book Reviews

The Autonomic Nervous System. By J. C. White and R. H. Smithwick. Price, $6.75. New York: The Macmillan Company, 1941.

This is a second revised edition of a deservedly popular book. The new material necessitated by the increase in knowledge and experience resulted in enlargement of the book by some 80 pages.

The historical introduction is interesting. Although the quotations from Claude Bernard are not, strictly speaking, in his "own words," nevertheless they will probably be more useful to most of those who will read the book than they would be in the original French. The chapter on anatomy is useful. It is convenient to have this information in such concise form; one regrets only that some of the illustrations have been reduced so much that their details can be followed only with a magnifying glass. The physiologic and pharmacologic chapters are not so useful, but the reader is consoled by the advice that if he is somewhat confused by the contradictory evidence presented, he can read all the arguments at much greater length in bigger books (references duly given) and, besides, that the important points will be emphasized later in the discussion of treatment of visceral disease. The method of these chapters has its advantages; after wading through page after page of historical references and conflicting opinions the reader is grateful and apt to remember when he comes finally to a definite statement such as that the "paralysis after denervation of smooth muscle is very different from that seen in skeletal muscle, because there is no lasting flaccid paralysis." The chapter on visceral pain is of commendable brevity and contains some useful clinical hints. Methods of study are described concisely and clearly.

With Part II the authors begin to speak not as the scribes and pharisees but as ones having authority. The authors have had the same difficulty with denervation of the upper extremity that has plagued other surgeons. The poor results they ascribe to subsequent hypersensitivity to epinephrine and to regeneration of nerves. To obviate these troubles they advise that one make as complete a preganglionic sympathectomy as possible and then try to prevent regeneration by wrapping the ganglia in a silk sheath; early results are said to be encouraging. The authors note the ineffectiveness of sympathectomy in treatment of diseases of the bones and joints, except for relief of pain or vasospastic complications. The effectiveness of ganglionectomy in treatment of causalgia and the occasional startling relief resulting from use of procaine block in such painful afflictions are noted. The treatment of epilepsy and retinitis pigmentosa by sympathectomy is dismissed as ineffective. For cases of severe angina pectoris interruption of the upper four thoracic dorsal roots, or of the sympathetic rami leading to them, is advised. The authors point out that all one can hope to accomplish by intervention on the autonomic system in cases of angina is to relieve pain. It is admitted that the method of action of sympathectomy in the relief of vascular hypertension is unknown, but the authors believe that it is very effective in selected cases and should be extensive to obtain the best results, regardless of the annoying subsequent postural hypotension. Sympathectomy for asthma is condemned. Although there is no evidence that the sympathetic supply plays any part in the autonomic reflex responses of the colon, the authors find that the ability of the large intestine to evacuate is improved after removal of its sympathetic nerves; it should not be forgotten, however, that medical treatment of congenital megacolon is increasingly effective. The authors agree that the sympathetic system plays no role in the activity of the urinary bladder. Presacral neurectomy does not improve the func-

tion of the atonic bladder, nor is it of much help to relieve pain originating in the bladder; this operation finds its greatest usefulness in the treatment of painful dysmenorrhea.

Part III is concerned with the technic of operations. Practically all of these are carried out on the sympathetic part of the autonomic system. The authors' experience has taught them that to produce lasting results the denervation must be anatomically complete and performed in such a way that regeneration cannot occur. And the power of the sympathetic nerves to regenerate is uncanny, even after removal of the bodies of the postganglionic neurons, but the afferent pain fibers which run in the sympathetic trunks do not have this ability to regenerate. The various operative procedures favored by the authors are clearly described and illustrated, as are the methods of paravertebral injection and peripheral sympathectomy.

The book is well printed on dull paper, which makes it easy to read. It can be heartily recommended as an authoritative guide for any one interested in this field of medicine. One has the impression on reading the book that the possibilities and limitations of operative relief of visceral disease are approaching a definitive formulation.

The Traumatic Neuroses of War. By Abram Kardiner. Psychosomatic Medicine Monograph II-III. Published with the Sponsorship of the Committee on Problems of Neurotic Behavior, Division of Anthropology and Psychology, National Research Council, Washington, D. C. Paper, $3; cloth, $3.50. Pp. 258. New York: Paul B. Hoeber, Inc., 1941.

This is an important publication for the present critical time and is of even greater importance now that the United States is actively participating in the war. Dr. Kardiner bases his concepts on the prolonged study of a large group of cases of neuroses that followed World War I.

He found that the concept of instinctual drives and defenses against them, which have been erected in order to maintain a satisfactory existence in childhood with parents and in adulthood with the superego, has contributed much to the understanding and therapy of the transference neuroses but is not of much value in the understanding and treatment of the war neuroses.

Instead, he found it more valuable to consider the war neuroses as the result of a disorder of the utility functioning of the ego. In this he relates them closely to the concept he evolved several years ago regarding epilepsy. The disorders of the utility function of the ego start with a painful traumatic experience. In order to avoid a repetition of the pain the patient inhibits this function and then attempts to adapt the inhibited ego to the purpose of living. His attempts at adaptation are seen in his symptoms. In a scholarly and logical manner the author develops his reasons for these concepts, starting with a description and then a penetrating analysis of the symptomatology of the war neuroses. He follows this with a discussion of the development of an effective ego and the relation between this and the symptomatology of the war neuroses. The third section is devoted to the practical application of these concepts to the diagnosis and treatment of the war neuroses.

Not only is this book a practical help to the psychiatrist if he should be called on to deal with war neuroses at present, but it is also a valuable contribution to a better understanding of ego psychology, about which too little is known. Dr. Kardiner is to be highly commended for this valuable and timely monograph.